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(54) Title: COMPOUNDS AND METHODS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER

(57) Abstract

Compounds and methods for the treatment and diagnosis of lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or DNA molecules encoding such polypeptides, are also provided, together with DNA molecules for preparing the inventive polypeptides.

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COMPOUNDS AND METHODS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment and diagnosis of lung cancer. The invention is more specifically related to nucleotide sequences that are preferentially expressed in lung tumor tissue, together with polypeptides encoded by such nucleotide sequences. The inventive nucleotide sequences and polypeptides may be used in vaccines and pharmaceutical compositions for the treatment and diagnosis of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and methods for the therapy of lung cancer. In a first aspect, isolated polynucleotide molecules encoding lung

tumor polypeptides are provided, such polynucleotide molecules comprising a nucleotide sequence selected from the group consisting of: (a) sequences provided in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171; (b) sequences complementary to a sequence provided in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171; and (b) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

In a second aspect, isolated polypeptides are provided that comprise at least an immunogenic portion of a lung tumor protein or a variant thereof. In specific embodiments, such polypeptides comprise an amino acid sequence encoded by a polynucleotide molecule comprising a nucleotide sequence selected from the group consisting of (a) sequences recited in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171; (b) sequences complementary to a sequence provided in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

In related aspects, expression vectors comprising the inventive polynucleotide molecules, together with host cells transformed or transfected with such expression vectors are provided. In preferred embodiments, the host cells are selected from the group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known lung tumor antigen, are provided.

The present invention further provides pharmaceutical compositions comprising one or more of the above polypeptides, fusion proteins or polynucleotide molecules and a physiologically acceptable carrier, together with vaccines comprising one or

more such polypeptides, fusion proteins or polynucleotide molecules in combination with an immune response enhancer.

In related aspects, the present invention provides methods for inhibiting the development of lung cancer in a patient, comprising administering to a patient an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

Additionally, the present invention provides methods for immunodiagnosis of lung cancer, together with kits for use in such methods. Polypeptides are disclosed which comprise at least an immunogenic portion of a lung tumor protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein the lung tumor protein comprises an amino acid sequence encoded by a polynucleotide molecule having a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171, and variants thereof. Such polypeptides may be usefully employed in the diagnosis and monitoring of lung cancer.

In one specific aspect of the present invention, methods are provided for detecting lung cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of lung cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of lung cancer.

The present invention further provides methods for detecting lung cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide molecule that encodes one of the above polypeptides; and (c) detecting in the sample a polynucleotide sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide molecule including a sequence selected from the group consisting of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171.

In a further aspect, the present invention provides a method for detecting lung cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide molecule that encodes one of the above polypeptides; and (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide molecule having a partial sequence selected from the group consisting of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154,157, 158, 160, 162-164, 167, 168 and 171.

In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

In yet a further aspect, methods for the treatment of lung cancer in a patient are provided, the methods comprising obtaining PBMC from the patient, incubating the PBMC with a polypeptide of the present invention (or a polynucleotide that encodes such a polypeptide) to provide incubated T cells and administering the incubated T cells to the patient. The present invention additionally provides methods for the treatment of lung cancer that comprise incubating antigen presenting cells with a polypeptide of the present invention (or a polynucleotide that encodes such a polypeptide) to provide incubated antigen presenting cells and administering the incubated antigen presenting cells to the patient. In certain embodiments, the antigen presenting cells are selected from the group consisting of dendritic cells and macrophages. Compositions for the treatment of lung cancer comprising T cells or antigen presenting cells that have been incubated with a polypeptide or polynucleotide of the

present invention are also provided. These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of lung cancer. The compositions described herein include polypeptides, fusion proteins and polynucleotide molecules. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In one aspect, the subject invention discloses polypeptides comprising an immunogenic portion of a human lung tumor protein, wherein the lung tumor protein includes an amino acid sequence encoded by a polynucleotide molecule including a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NO: 1-109, , 111, 113 115-151, 153, 154,157, 158, 160, 162-164, 167, 168 and 171, (b) the complements of said nucleotide sequences, and (c) variants of such sequences. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above lung tumor proteins may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may (but need not) be immunoreactive and/or antigenic. As detailed below, such polypeptides may be isolated from lung tumor tissue or prepared by synthetic or recombinant means.

As used herein, an "immunogenic portion" of a lung tumor protein is a portion that is capable of eliciting an immune response in a patient inflicted with lung cancer and as such binds to antibodies present within sera from a lung cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays

may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of lung cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides. A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the therapeutic, antigenic and/or immunogenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably

exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as describe below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications. including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA, 2*:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The antigens provided by the present invention include variants that are encoded by polynucleotide sequences which are substantially homologous to one or more of the polynucleotide sequences specifically recited herein. "Substantial homology," as used herein, refers to polynucleotide sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a

solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing polynucleotide sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing polynucleotide sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad., Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Also included in the scope of the present invention are alleles of the genes encoding the nucleotide sequences recited in herein. As used herein, an "allele" or "allellic sequence" is an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given gene may have none, one, or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone or in combination with the others, one or more times in a given sequence.

For lung tumor polypeptides with immunoreactive properties, variants may, alternatively, be identified by modifying the amino acid sequence of one of the above polypeptides, and evaluating the immunoreactivity of the modified polypeptide. For lung tumor polypeptides useful for the generation of diagnostic binding agents, a variant may be identified by evaluating a modified polypeptide for the ability to generate antibodies that detect the presence or absence of lung cancer. Such modified sequences may be prepared and tested using, for example, the representative procedures described herein.

The lung tumor polypeptides of the present invention, and polynucleotide molecules encoding such polypeptides, may be isolated from lung tumor tissue using any of a variety of methods well known in the art. Polynucleotide sequences corresponding to a gene

(or a portion thereof) encoding one of the inventive lung tumor proteins may be isolated from a lung tumor cDNA library using a subtraction technique as described in detail below. Examples of such polynucleotide sequences are provided in SEQ ID NO: 1-109,111,113 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171. Partial polynucleotide sequences thus obtained may be used to design oligonucleotide primers for the amplification of full-length polynucleotide sequences from a human genomic DNA library or from a lung tumor cDNA library in a polymerase chain reaction (PCR), using techniques well known in the art (see, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol. 51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989). For this approach, sequence-specific primers may be designed based on the nucleotide sequences provided herein and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (*e.g.*, a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length

cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using techniques well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol. 51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989), and software well known in the art may also be employed. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Transcription-Mediated Amplification, or TMA is another method that may be utilized for the amplification of DNA, rRNA, or mRNA, as described in Patent No. PCT/US91/03184. This autocatalytic and isothermic non-PCR based method utilizes two primers and two enzymes: RNA polymerase and reverse transcriptase. One primer contains a promoter sequence for RNA polymerase. In the first amplification, the promoter-primer hybridizes to the target rRNA at a defined site. Reverse transcriptase creates a DNA copy of the target rRNA by extension from the 3'end of the promoter-primer. The

RNA in the resulting complex is degraded and a second primer binds to the DNA copy. A new strand of DNA is synthesized from the end of the primer by reverse transcriptase creating double stranded DNA. RNA polymerase recognizes the promoter sequence in the DNA template and initiates transcription. Each of the newly synthesized RNA amplicons re-enters the TMA process and serves as a template for a new round of replication leading to the expotential expansion of the RNA amplicon. Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Once a polynucleotide sequence encoding a polypeptide is obtained, the polypeptide may be produced recombinantly by inserting the polynucleotide sequence into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polynucleotide molecule that encodes the recombinant polypeptide. Suitable host cells include prokaryotes, yeast, insect and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as COS or CHO cells. The polynucleotide sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof. Supernatants from suitable host/vector systems which secrete the recombinant polypeptide may first be concentrated using a commercially available filter. The concentrate may then be applied to a suitable purification matrix, such as an affinity matrix or ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify the recombinant polypeptide.

The lung tumor polypeptides disclosed herein may also be generated by synthetic means. In particular, synthetic polypeptides having fewer than about 100 amino

acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In addition, lung tumor antigens may be identified by T cell expression cloning. One source of tumor specific T cells is from surgically excised tumors from human patients. In one method for isolating and characterizing tumor specific T cells, the excised tumor is minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells are washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands are harvested from the interfaces; the upper band at the 75%/HBSS interface contains predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contains a majority of lymphocytes. The TILs are expanded in culture by techniques well known in the art, but preferably in culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, cultured and expanded in tissue culture plates that have been pre-adsorbed with anti-CD3 monoclonal antibody (OKT3). The resulting TIL cultures are analyzed by FACS to confirm that the vast majority are CD8+ T cells (>90% of gated population).

In addition, the tumor cells are also expanded in culture using standard techniques well known in the art to establish a tumor cell line, which is later confirmed to be lung carcinoma cells by immunohistochemical analysis. The tumor cell line is transduced with a retroviral vector to express human CD80. The tumor cell line is further characterized by FACS analysis to confirm the strong expression levels of CD80, class I and II MHC molecules.

The specificity of the TIL lines to lung tumor is confirmed by INF-γ and/or TNF-α cytokine release assays. For example, TIL cells from day 21 cultures are co-cultured

with either autologous or allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562 and the culture supernatant monitored by ELISA for the presence of cytokines. The expression of these specific cytokines in the presence of tumor or negative control cells indicates whether the TIL lines are tumor specific and potentially recognizing tumor antigen presented by the autologous MHC molecules.

The characterized tumor-specific TIL lines can be expanded and cloned by methods well known in the art. For example, the TIL lines may be expanded to suitable numbers for T cell expression cloning by using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2. Clones from the expanded TIL lines can be generated by standard limiting dilution techniques. In particular, TIL cells are seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. These clones may be further analyzed for tumor specificity by ^{51}Cr microcytotoxicity and IFN-γ bioassays. Additionally, the MHC restriction element recognized by the TIL clones may be determined by antibody blocking studies well known in the art.

The CTL lines or clones described above may be employed to identify tumor specific antigens. For example, autologous fibroblasts or LCL from a patient may be transfected or transduced with polynucleotide fragments derived from a lung tumor cDNA library to generate target cells expressing tumor polypeptides. The target cells expressing tumor polypeptides in the context of MHC will be recognized by the CTL line or clone resulting in T-cell activation, which can be monitored by cytokine detection assays. The tumor gene being expressed by the target cell and recognized by the tumor-specific CTL is then isolated by techniques described above. In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides

are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known lung tumor antigen, together with variants of such fusion proteins. The fusion proteins of the present invention may (but need not) include a linker peptide between the first and second polypeptides.

A polynucleotide sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate polynucleotide sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second

polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated polynucleotide sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of polynucleotide are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91 (1997)).

Polypeptides of the present invention that comprise an immunogenic portion of a lung tumor protein may generally be used for therapy of lung cancer, wherein the polypeptide stimulates the patient's own immune response to lung tumor cells. The present invention thus provides methods for using one or more of the compounds described herein (which may be polypeptides, polynucleotide molecules or fusion proteins) for immunotherapy of lung cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with disease, or may be free of detectable disease. Accordingly, the compounds disclosed herein may be used to treat lung cancer or to inhibit the development of lung cancer. The compounds are preferably administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the inventive polypeptide is generally present within a pharmaceutical composition or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more such polypeptides and a non-specific immune-response enhancer, wherein the non-specific immune response enhancer is capable of eliciting or enhancing an immune response to an exogenous antigen. Examples of non-specific-immune response enhancers include

adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of lung tumor antigens, either incorporated into a fusion protein as described above (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain polynucleotide encoding one or more of the above polypeptides and/or fusion proteins, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary polynucleotide sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a lung cell antigen on its cell surface. In a preferred embodiment, the polynucleotides may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *PNAS 91*:215-219, 1994; Kass-Eisler et al., *PNAS 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating polynucleotide into such expression systems are well known to those of ordinary skill in the art. The polynucleotides may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science 259*:1745-1749, 1993, reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked polynucleotides may be increased by coating the polynucleotides onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or polynucleotide that is effective to raise an immune response (cellular and/or humoral) against lung tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the polynucleotide molecule(s) in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of immune-response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially

available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).Polypeptides and polynucleotides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

In passive immunotherapy, treatment involves the delivery of biologic reagents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, gamma/delta T lymphocytes, tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. These *in vitro* culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above, the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast, or B-cells, may be pulsed with immunoreactive polypeptides, or polynucleotide sequence(s) may be introduced into antigen presenting cells, using a variety of standard techniques well known in the art. For example, antigen presenting cells may be transfected or transduced with a polynucleotide sequence,

wherein said sequence contains a promoter region appropriate for increasing expression, and can be expressed as part of a recombinant virus or other expression system. Several viral vectors may be used to transduce an antigen presenting cell, including pox virus, vaccinia virus, and adenovirus; also, antigen presenting cells may be transfected with polynucleotide sequences disclosed herein by a variety of means, including gene-gun technology, lipid-mediated delivery, electroporation, osmotic shock, and particlate delivery mechanisms, resulting in efficient and acceptable expression levels as determined by one of ordinary skill in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term *in vivo*. Studies have demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever, M., *et al*, "Therapy With Cultured T Cells: Principles Revisited," *Immunological Reviews, 157*:177, 1997).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang *et al, (Crit. Rev. Oncol. Hematol., 22*(3), 213, 1996). Cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using

standard techniques and the cells are administered back to the patient.

In other embodiments, T-cell and/or antibody receptors specific for the polypeptides disclosed herein can be cloned, expanded, and transferred into other vectors or effector cells for use in adoptive immunotherapy. In particular, T cells may be transfected with the appropriate genes to express the variable domains from tumor specific monoclonal antibodies as the extracellular recognition elements and joined to the T cell receptor signaling chains, resulting in T cell activation, specific lysis, and cytokine release. This enables the T cell to redirect its specificity in an MHC-independent manner. See for example, Eshhar, Z., *Cancer Immunol Immunother*, 45(3-4):131-6, 1997 and Hwu, P., et al, *Cancer Res*, 55(15):3369-73, 1995. Another embodiment may include the transfection of tumor antigen specific alpha and beta T cell receptor chains into alternate T cells, as in Cole, DJ, et al, *Cancer Res*, 55(4):748-52, 1995.

In a further embodiment, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al, *Immunological Reviews, 157*:177, 1997).

Furthermore, vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

Additionally, vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient. Polypeptides and fusion proteins of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human lung tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein.

Binding agents are capable of differentiating between patients with and without lung cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a lung tumor protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic lung cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic lung cancer. Suitable portions of such lung tumor proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic lung cancer in substantially all (*i.e.*, at least about 80%, and preferably at least about 90%) of the patients for which lung cancer would be indicated using the full length protein, and that indicate the absence of lung cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human lung tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human lung tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic lung cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic lung tumors by such procedures are considered to be useful in assays for detecting primary or metastatic human lung tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human lung tumors may be used as markers for diagnosing lung cancer or for monitoring disease progression in patients. In one embodiment, lung cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above

polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera, urine and/or lung secretions.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a

polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without lung cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for lung cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for lung cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of lung cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of lung cancer. In this embodiment, assays as described above for the diagnosis of lung cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, lung cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, lung cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* *6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield,

such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate lung tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin. Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the

catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing

nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Diagnostic reagents of the present invention may also comprise polynucleotide sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify lung tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide molecule encoding a lung tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide molecule encoding a lung tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide molecule" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide molecule in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a polynucleotide molecule comprising sequence selected from SEQ ID NO: 1-109, 111, 113 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide molecule comprising a sequence provided in SEQ ID NO: 1-109,111, 113 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171. Techniques for both PCR based assays and hybridization assays are

well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect lung tumor-specific sequences in biological samples, including blood, semen, lung tissue and/or lung tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

ISOLATION AND CHARACTERIZATION OF cDNA SEQUENCES ENCODING LUNG TUMOR POLYPEPTIDES

This example illustrates the isolation of cDNA molecules encoding lung tumor-specific polypeptides from lung tumor cDNA libraries.

A. Isolation of cDNA Sequences from a Lung Squamous Cell Carcinoma Library

A human lung squamous cell carcinoma cDNA expression library was constructed from poly A^+ RNA from a pool of two patient tissues using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD) following the manufacturer's protocol. Specifically, lung carcinoma tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A^+ RNA was then purified using an oligo dT cellulose column as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with BstXI/EcoRI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with cDNA size fractionation columns (BRL Life Technologies), the cDNA was ligated into the BstXI/NotI

site of pcDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human lung cDNA expression library was prepared from a pool of four tissue specimens. The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The lung squamous cell carcinoma library contained 2.7 x 10^6 independent colonies, with 100% of clones having an insert and the average insert size being 2100 base pairs. The normal lung cDNA library contained 1.4 x 10^6 independent colonies, with 90% of clones having inserts and the average insert size being 1800 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA

cDNA library subtraction was performed using the above lung squamous cell carcinoma and normal lung cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a lung squamous cell carcinoma-specific subtracted cDNA library was generated as follows. Normal tissue cDNA library (80 μg) was digested with BamHI and XhoI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 133 μl of H_2O, heat-denatured and mixed with 133 μl (133 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (67 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H_2O to form the driver DNA.

To form the tracer DNA, 10 μg lung squamous cell carcinoma cDNA library was digested with NotI and SpeI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech, Palo Alto, CA). Typically, 5 μg of cDNA was recovered after the sizing column. Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H_2O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred

into a 68 ^{0}C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 µl H_2O, mixed with 8 µl driver DNA and 20 µl of 2 x hybridization buffer, and subjected to a hybridization at 68 ^{0}C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into NotI/SpeI site of chloramphenicol resistant pBCSK$^+$ (Stratagene, La Jolla, CA) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a lung squamous cell carcinoma specific subtracted cDNA library (herein after referred to as "lung subtraction I").

A second lung squamous cell carcinoma specific subtracted cDNA library (referred to as "lung subtraction II") was generated in a similar way to the lung subtraction library I, except that eight frequently recovered genes from lung subtraction I were included in the driver DNA, and 24,000 independent clones were recovered.

To analyze the subtracted cDNA libraries, plasmid DNA was prepared from 320 independent clones, randomly picked from the subtracted lung squamous cell carcinoma specific libraries. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A and/or Model 377 (Foster City, CA). The cDNA sequences for sixty isolated clones are provided in SEQ ID NO: 1-60. These sequences were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). No significant homologies were found to the sequences provided in SEQ ID NO: 2, 3, 19, 38 and 46. The sequences of SEQ ID NO: 1, 6-8, 10-13, 15, 17, 18, 20-27, 29, 30, 32, 34-37, 39-45, 47-49, 51, 52, 54, 55 and 57-59 were found to show some homology to previously identified expressed sequence tags (ESTs). The sequences of SEQ ID NO: 9, 28, 31 and 33 were found to show some homology to previously identified non-human gene sequences and the sequences of SEQ ID NO: 4, 5, 14, 50, 53, 56 and 60 were found to show some homology to gene sequences previously identified in humans.

The subtraction procedure described above was repeated using the above lung squamous cell carcinoma cDNA library as the tracer DNA, and the above normal lung tissue cDNA library and a cDNA library from normal liver and heart (constructed from a pool of

one sample of each tissue as described above), plus twenty other cDNA clones that were frequently recovered in lung subtractions I and II, as the driver DNA (lung subtraction III). The normal liver and heart cDNA library contained 1.76 x 10^6 independent colonies, with 100% of clones having inserts and the average insert size being 1600 base pairs. Ten additional clones were isolated (SEQ ID NO: 61-70). Comparison of these cDNA sequences with those in the gene bank as described above, revealed no significant homologies to the sequences provided in SEQ ID NO: 62 and 67. The sequences of SEQ ID NO: 61, 63-66, 68 and 69 were found to show some homology to previously isolated ESTs and the sequence provided in SEQ ID NO: 70 was found to show some homology to a previously identified rat gene.

B. Isolation of cDNA Sequences from a Lung Adenocarcinoma Library

A human lung adenocarcinoma cDNA expression library was constructed as described above. The library contained 3.2 x 10^6 independent colonies, with 100% of clones having an insert and the average insert size being 1500 base pairs. Library subtraction was performed as described above using the normal lung and normal liver and heart cDNA expression libraries described above as the driver DNA. Twenty-six hundred independent clones were recovered.

Initial cDNA sequence analysis from 100 independent clones revealed many ribosomal protein genes. The cDNA sequences for fifteen clones isolated in this subtraction are provided in SEQ ID NO: 71-86. Comparison of these sequences with those in the gene bank as described above revealed no significant homologies to the sequence provided in SEQ ID NO: 84. The sequences of SEQ ID NO: 71, 73, 74, 77, 78 and 80-82 were found to show some homology to previously isolated ESTs, and the sequences of SEQ ID NO: 72, 75, 76, 79, 83 and 85 were found to show some homology to previously identified human genes.

Example 2

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for seven representative lung tumor polypeptides described in Example 1 were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous cell carcinoma from 3 patients, lung adenocarcinoma, colon tumor from 2 patients, breast tumor and prostate tumor), and thirteen different normal tissues (lung from 4 donors, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, stomach, myocardium, retina and testes). Using a 10-fold amount of cDNA, the antigen LST-S1-90 (SEQ ID NO: 3) was found to be expressed at high levels in lung squamous cell carcinoma and in breast tumor, and at low to undetectable levels in the other tissues examined.

The antigen LST-S2-68 (SEQ ID NO: 15) appears to be specific to lung and breast tumor, however, expression was also detected in normal kidney. Antigens LST-S1-169 (SEQ ID NO: 6) and LST-S1-133 (SEQ ID NO: 5) appear to be very abundant in lung tissues (both normal and tumor), with the expression of these two genes being decreased in most of the normal tissues tested. Both LST-S1-169 and LST-S1-133 were also expressed in breast and colon tumors. Antigens LST-S1-6 (SEQ ID NO: 7) and LST-S2-I2-5F (SEQ ID NO: 47) did not show tumor or tissue specific expression, with the expression of LST-S1-28 being rare and only detectable in a few tissues. The antigen LST-S3-7 (SEQ ID NO: 63) showed lung and breast tumor specific expression, with its message only being detected in

normal testes when the PCR was performed for 30 cycles. Lower level expression was detected in some normal tissues when the cycle number was increased to 35. Antigen LST-S3-13 (SEQ ID NO: 66) was found to be expressed in 3 out of 4 lung tumors, one breast tumor and both colon tumor samples. Its expression in normal tissues was lower compared to tumors, and was only detected in 1 out of 4 normal lung tissues and in normal tissues from kidney, ovary and retina. Expression of antigens LST-S3-4 (SEQ ID NO: 62) and LST-S3-14 (SEQ ID NO: 67) was rare and did not show any tissue or tumor specificity. Consistent with Northern blot analyses, the RT-PCT results on antigen LAT-S1-A-10A (SEQ ID NO: 78) suggested that its expression is high in lung, colon, stomach and small intestine tissues, including lung and colon tumors, whereas its expression was low or undetectable in other tissues.

A total of 2002 cDNA fragments isolated in lung subtractions I, II and III, described above, were colony PCR amplified and their mRNA expression levels in lung tumor, normal lung, and various other normal and tumor tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Seventeen non-redundant cDNA clones showed over-expression in lung squamous tumors, with expression in normal tissues tested (lung, skin, lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland) being either undetectable, or 10-fold less compared to lung squamous tumors. The determined partial cDNA sequences for the clone L513S are provided in SEQ ID NO: 87 and 88; those for L514S are provided in SEQ ID NO: 89 and 90; those for L516S in SEQ ID NO: 91 and 92; that for L517S in SEQ ID NO: 93; that for L519S in SEQ ID NO: 94; those for L520S in SEQ ID NO: 95 and 96; those for L521S in SEQ ID NO: 97 and 98; that for L522S in SEQ ID NO: 99; that for L523S in SEQ ID NO: 100; that for L524S in SEQ ID NO: 101; that for L525S in SEQ ID NO: 102; that for L526S in SEQ ID NO: 103; that for L527S in SEQ ID NO: 104; that for L528S in

SEQ ID NO: 105; that for L529S in SEQ ID NO: 106; and those for L530S in SEQ ID NO: 107 and 108. Additionally, the full-length cDNA sequences for L503S and L514S (variants 1 and 2), are provided in SEQ ID NO: 151, 153 and 154, respectively, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 152, 155 and 156. Due to polymorphisms, the clone L531S appears to have two forms. A first determined full-length cDNA sequence for L531S is provided in SEQ ID NO: 109, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 110. A second determined full-length cDNA sequence for L531S is provided in SEQ ID NO: 111, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 112. The sequence of SEQ ID NO: 111 is identical to that of SEQ ID NO: 109, except that it contains a 27 bp insertion. Similarly, L514S also has two alternatively spliced forms; the first variant cDNA is listed as SEQ ID NO: 153, with the corresponding amino acid sequence as SEQ ID NO: 155. The second variant form of L514S full-length cDNA is referred to as SEQ ID NO: 154, with its corresponding amino acid sequence as SEQ ID NO: 156.

Full length cloning for L524S (SEQ ID NO: 101) yielded two variants (SEQ ID NO: 163 and 164) with the corresponding predicted amino acid sequences (SEQ ID NO: 165 and 166), respectively. Both variants have been shown to encode parathyroid hormone-related peptide.

Comparison of the sequences of L514S and L531S (SEQ ID NO: 87 and 88, 89 and 90, and 109, respectively) with those in the gene bank, as described above, revealed no significant homologies to known sequences. The sequences of L513S, L516S, L517S, L519S, L520S and L530S (SEQ ID NO: 87 and 88, 91 and 92, 93, 94, 95 and 96, 107 and 108, respectively) were found to show some homology to previously identified ESTs. The sequences of L521S, L522S, L523S, L524S, L525S, L526S, L527S, L528S and L529S (SEQ ID NO: 97 and 98, 99, 99, 101, 102, 103, 104, 105, and 106, respectively) were found to represent known genes. The determined full-length cDNA sequences for L520S is provided in SEQ ID NO: 113, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 114. Subsequent microarray analysis has shown L520S to be overexpressed in breast tumors in addition to lung squamous tumors.

Further analysis has demonstrated L529S (SEQ ID NO: 106 and 115), L525S (SEQ ID NO: 102 and 120) and L527S (SEQ ID NO: 104) are cytosleletal components and potentially squamous cell specific proteins. L529S is connexin 26, a gap junction protein. It is highly expressed in lung squamous tumor 9688T, and moderately over-expressed in two others. However, lower level expression of connexin 26 is also detectable in normal skin, colon, liver and stomach. The over-expression of connexin 26 in some breast tumors has been reported and a mutated form of L529S may result in over-expression in lung tumors. L525S is plakophilin 1, a desmosomal protein found in plaque-bearing adhering junctions of the skin. Expression levels for L525S mRNA is highly elevated in three out of four lung squamous tumors tested, and in normal skin. L527S has been identified as keratin 6 isoform, type II 58 Kd keratin, and cytokeratin 13 and shows over-expression in squamous tumors and low expression in normal skin, breast and colon tissues. Notably, keratin and keratin-related genes have been extensively documented as potential markers for lung cancer including CYFRA2.1 (Pastor, A., et al, *Eur. Respir. J.*, 10:603-609, 1997). L513S (SEQ ID NO: 87 and 88) shows moderate over-expression in several tumor tissues tested, and encodes a protein that was first isolated as a pemphigus vulgaris antigen.

L520S (SEQ ID NO: 95 and 96) and L521S (SEQ ID NO: 97 and 98) are highly expressed in lung squamous tumors, and L520S is up-regulated in normal salivary gland and L521S is over-expressed in normal skin. Both belong to a family of small proline rich proteins and represent markers for fully differentiated squamous cells. L521S has been described as a specific marker for lung squamous tumor (Hu, R., et al, *Lung Cancer*, 20:25-30, 1998). L515S (SEQ ID NO: 162) encodes IGF-β2 and L516S is an aldose reductase homologue and both are moderately expressed in lung squamous tumors and in normal colon. Notably, L516S (SEQ ID NO: 91 and 92) is up-regulated in metastatic tumors but not primary lung adenocarcinoma., an indication of its potential role in metatasis and a potential prognostic marker. L522S (SEQ ID NO: 99) is moderately over-expressed in lung squamous tumors with minimum expression in normal tissues. L522S has been shown to belong to a class IV alcohol dehydrogenase, ADH7, and its expression profile suggests it is a squamous cell specific antigen. L523S (SEQ ID NO: 100) is moderately over-expressed in lung

squamous tumor, human pancreatic cancer cell lines and pancreatic cancer tissues, suggesting this gene may be a shared antigen between pancreatic and lung squamous cell cancer.

L524S (SEQ ID NO: 101) is over-expressed in the majority of squamous tumors tested and is homolgous with parathyroid hormone-related peptide (PTHrP), which is best known to cause humoral hypercalcaemia associated with malignant tumors such as leukemia, prostate and breast cancer. It is also believed that PTHrP is most commonly associated with squamous carcinoma of lung and rarely with lung adenocarcinoma (Davidson, L.A., et al, *J. Pathol.*, 178: 398-401, 1996). L528S (SEQ ID NO: 105) is highly over-expressed in two lung squamous tumors with moderate expression in two other squamous tumors, one lung adenocarcinoma and some normal tissues, including skin, lymph nodes, heart, stomach and lung. It encodes the NMB gene that is similar to the precursor of melanocyte specific gene Pmel17, wfhich is reported to be preferentially expressed in low-metastatic potential melanoma cell lines. This suggests that L528S may be a shared antigen in both melanoma and lung aquamous cell carcinoma. L526S (SEQ ID NO: 103) is overexpressed in all lung squamous cell tumor tissues tested and has been shown to share homology with a gene (ATM) in which a mutation causes ataxia telangiectasia, a genetic disorder in humans causing a predisposition to cancer, among other symptoms. ATM encodes a protein that activates p53 mediated cell-cycle checkpoint through direct binding and phosphorylation of the p53 molecule. Approximately 40% of lung cancer is associated with p53 mutations, and it is speculated that over-expression of ATM is a result of compensation for loss of p53 function, but it is unknown whether over-expression is the cause of result of lung squamous cell carcinoma. Additionally, expression of L526S (ATM) is also detected in a metastatic but not lung adenocarcinoma, suggesting a role in metastasis.

Example 3

ISOLATION AND CHARACTERIZATION OF LUNG TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

Eight hundred and fifty seven clones from a cDNA subtraction library, containing cDNA from a pool of two human lung squamous tumors subtracted against eight

normal human tissue cDNAs including lung, PBMC, brain, heart, kidney, liver, pancreas, and skin, (Clontech, Palo Alto, CA) were derived and submitted to a first round of PCR amplification. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector P7- Adv vector (Clontech, Palo Alto, CA) and transformed into DH5α *E. coli* (Gibco, BRL). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

One hundred and sixty two positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank using the EMBL and GenBank databases, as described above, revealed no significant homologies to 13 of these clones, hereinafter referred to as Contig 13, 16, 17, 19, 22, 24, 29, 47, 49, 56-59 . The determined cDNA sequences for these clones are provided in SEQ ID NO: 125, 127-129, 131-133, 142, 144, 148-150, and 157, respectively. Contigs 1, 3-5, 7-10, 12, 11, 15, 20, 31, 33, 38, 39, 41, 43, 44, 45, 48, 50, 53, 54 (SEQ ID NO: 115-124, 126, 130, 134-141, 143, 145-147, respectively) were found to show some degree of homology to previously identified DNA sequences. Contig 57 (SEQ ID NO: 149) was found to represent the clone L519S (SEQ ID NO: 94) disclosed in US. Patent Application No. 09/123,912, filed July 27, 1998. To the best of the inventors' knowledge, none of these sequences have been previously shown to be differentially over-expressed in lung tumors.

mRNA expression levels for representative clones in lung tumor tissues, normal lung tissues (n=4), resting PBMC, salivary gland, heart, stomach, lymph nodes, skeletal muscle, soft palate, small intestine, large intestine, bronchial, bladder, tonsil, kidney, esophagus, bone marrow, colon, adrenal gland, pancreas, and skin, (all derived from human) were determined by RT-PCR as described above. Expression levels using microarray technology, as described above, were examined in one sample of each tissue type unless otherwise indicated.

Contig 3 (SEQ ID NO: 116) was found to be highly expressed in all head and neck squamous cell tumors tested (17/17), and expressed in the majority (8/12) of lung squamous tumors, (high expression in 7/12, moderate in 2/12, and low in 2/12), while showing negative expression for 2/4 normal lung tissues and low expression in the remaining

two samples. Contig 3 showed moderate expression in skin and soft palate, and lowered expression levels in resting PBMC, large intestine, salivary gland, tonsil, pancreas, esophagus, and colon. Contig 11 (SEQ ID NO: 124) was found to be expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 14/17, and moderately expressed in 3/17. Additionally, expression in lung squamous tumors showed high expression in 3/12 and moderate in 4/12. Contig 11 was negative for 3/4 normal lung samples, with the remaining sample having only low expression. Contig 11 showed low to moderate reactivity to salivary gland, soft palate, bladder, tonsil, skin, esophagus, and large intestine. Contig 13 (SEQ ID NO: 125) was found to be expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 12/17, and moderately expressed in 5/17. Contig 13 was expressed in 7/12 lung squamous tumors, with high expression in 4/12 and moderate expression in three samples. Analysis of normal lung samples showed negative expression for 2/4 and low to moderate expression in the remaining two samples. Contig 13 did show low to moderate reactivity to resting PBMC, salivary gland, bladder, pancreas, tonsil, skin, esophagus, and large intestine, as well as high expression in soft palate. Contig 16 (SEQ ID NO: 127) was found to be moderately expressed in some head and neck squamous cell tumors (6/17) and one lung squamous tumor; while showing no expression in any normal lung samples tested. Contig 16 did show low reactivity to resting PBMC, large intestine, skin, salivary gland, and soft palate. Contig 17 (SEQ ID NO: 128) was shown to be expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 5/17, and moderately expressed in 12/17. Expression levels in lung squamous tumors showed one tumor sample with high expression and 3/12 with moderate levels. Contig 17 was negative for 2/4 normal lung samples, with the remaining samples having only low expression. Additionally, low level expression was found in esophagus and soft palate. Contig 19 (SEQ ID NO: 129) was found to be expressed in most head and neck squamous cell tumors tested (11/17): with two samples having high levels, 6/17 showing moderate expression, and low expression being found in 3/17. Testing in lung squamous tumors revealed only moderate expression in 3/12 samples. Expression levels in 2/4 of normal lung samples were negative, the two other samples having only low expression. Contig 19 did show low expression levels in esophagus, resting PBMC, salivary gland, bladder, soft palate, and pancreas.

Contig 22, (SEQ ID NO: 131) was shown to be expressed in most head and neck squamous cell tumors tested (13/17) with high expression in four of these samples, moderate expression in 6/17, and low expression in 3/17. Expression levels in lung squamous tumors were found to be moderate to high for 3/12 tissues tested, with negative expression in two normal lung samples and low expression in two other samples (n=4). Contig 22 did show low expression in skin, salivary gland and soft palate. Similarly, Contig 24 (SEQ ID NO: 132) was found to be expressed in most head and neck squamous cell tumors tested (13/17) with high expression in three of these samples, moderate expression in 6/17, and low expression in 4/17. Expression levels in lung squamous tumors were found to be moderate to high for 3/12 tissues tested, with negative expression for three normal lung samples and low expression in one sample (n=4). Contig 24 did show low expression in skin, salivary gland and soft palate. Contig 29 (SEQ ID NO: 133) was expressed in nearly all head and neck squamous cell tumors tested (16/17): highly expressed in 4/17, moderately expressed in 11/17, with low expression in one sample. Also, it was moderately expressed in 3/12 lung squamous tumors, while being negative for 2/4 normal lung samples. Contig 29 showed low to moderate expression in large intestine, skin, salivary gland, pancreas, tonsil, heart and soft palate. Contig 47 (SEQ ID NO: 142) was expressed in most head and neck squamous cell tumors tested (12/17): moderate expression in 10/17, and low expression in two samples. In lung squamous tumors, it was highly expressed in one sample and moderately expressed in two others (n=13). Contig 47 was negative for 2/4 normal lung samples, with the remaining two samples having moderate expression. Also, Contig 47 showed moderate expression in large intestine, and pancreas, and low expression in skin, salivary gland, soft palate, stomach, bladder, resting PBMC, and tonsil.

Contig 48 (SEQ ID NO: 143) was expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 8/17 and moderately expressed in 7/17, with low expression in two samples. Expression levels in lung squamous tumors were high to moderate in three samples (n=13). Contig 48 was negative for one out of four normal lung samples, the remaining showing low or moderate expression. Contig 48 showed moderate expression in soft palate, large intestine, pancreas, and bladder, and low expression in esophagus, salivary gland, resting PBMC, and heart. Contig 49 (SEQ ID NO: 144) was

expressed at low to moderate levels in 6/17 head and neck squamous cell tumors tested. Expression levels in lung squamous tumors were moderate in three samples (n=13). Contig 49 was negative for 2/4 normal lung samples, the remaining samples showing low expression. Moderate expression levels in skin, salivary gland, large intestine, pancreas, bladder and resting PBMC were shown, as well as low expression in soft palate, lymph nodes, and tonsil. Contig 56 (SEQ ID NO: 148) was expressed in low to moderate levels in 3/17 head and neck squamous cell tumors tested, and in lung squamous tumors, showing low to moderate levels in three out of thirteen samples. Notably, low expression levels were detected in one adenocarcinoma lung tumor sample (n=2). Contig 56 was negative for 3/4 normal lung samples, and showed moderate expression levels in only large intestine, and low expression in salivary gland, soft palate, pancreas, bladder, and resting PBMC. Contig 58, also known as L769P, (SEQ ID NO: 150) was expressed at moderate levels in 11/17 head and neck squamous cell tumors tested and low expression in one additional sample. Expression in lung squamous tumors showed low to moderate levels in three out of thirteen samples. Contig 58 was negative for 3/4 normal lung samples, with one sample having low expression. Moderate expression levels in skin, large intestine, and resting PBMC were demonstrated, as well as low expression in salivary gland, soft palate, pancreas, and bladder. Contig 59 (SEQ ID NO: 157) was expressed in some head, neck, and lung squamous tumors. Low level expression of Contig 59 was also detected in salivary gland and large intestine.

Additionally, the full-length cDNA sequence for Contigs 22, referred to as L763P, is provided in SEQ ID NO: 158, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 159. Also, the full-length cDNA sequence incorporating Contigs 17, 19, and 24, referred to as L762P, is provided in SEQ ID NO: 160, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 161. Further analysis of L762P has determined it to be a type I membrane protein and two additional variants have been sequenced. Variant 1 (SEQ ID NO: 167 and the corresponding amino acid sequence in SEQ ID NO: 169) is an alternatively spliced form of SEQ ID NO: 160 resulting in deletion of 503 nucleotides, as well as deletion of a short segment of the expressed protein. Variant 2 (SEQ ID NO: 168 and the corresponding amino acid sequence

in SEQ ID NO: 170) has a two nucleotide deletion at the 3' coding region in comparison to SEQ ID NO: 160, resulting in a secreted form of the expressed protein.

The full-length cDNA sequence for contig 56 (SEQ ID NO: 148), referred to as L773P, is provided in SEQ ID NO: 171, with the predicted amino acid sequence in SEQ ID NO: 172. Subsequent Northern blot analysis of L773P demonstrates this transcript is differentially over-expressed in squamous tumors and detected at approximately 1.6 Kb in primary lung tumor tissue and approximately 1.3 Kb in primary head and neck tumor tissue.

Subsequent microarray analysis has shown Contig 58, also referred to as L769S (SEQ ID NO: 150), to be overexpressed in breast tumors in addition to lung squamous tumors.

Example 4
SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS:

1. An isolated polynucleotide molecule comprising a nucleotide sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171;

(b) the complements of sequences provided in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171; and

(c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

2. An isolated polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule of claim 1.

3. An isolated polynucleotide molecule comprising a nucleotide sequence encoding the polypeptide of claim 2.

4. An expression vector comprising an isolated polynucleotide molecule of claims 1 or 3.

5. A host cell transformed with the expression vector of claim 4.

6. The host cell of claim 5 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.

7. A pharmaceutical composition comprising the polypeptide of claim 2 and a physiologically acceptable carrier.

8. A vaccine comprising the polypeptide of claim 2 and a non-specific immune response enhancer.

9. The vaccine of claim 8 wherein the non-specific immune response enhancer is an adjuvant.

10. A vaccine comprising an isolated polynucleotide molecule of claims 1 or 3 and a non-specific immune response enhancer.

11. The vaccine of claim 10 wherein the non-specific immune response enhancer is an adjuvant.

12. A pharmaceutical composition for the treatment of lung cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85 , 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164;

(b) sequences complementary to the sequences of SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164 ; and

(c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

13. A vaccine for the treatment of lung cancer comprising a polypeptide and a non-specific immune response enhancer, said polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164;

(b) sequences complementary to the sequences of SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164; and

(c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

14. A vaccine for the treatment of lung cancer comprising a DNA molecule and a non-specific immune response enhancer, the polynucleotide molecule comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164;

(b) sequences complementary to the sequences of SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164; and

(c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

15. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claims 7 or 12.

16. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of any one of claims 8, 10, 13 or 14.

17. A fusion protein comprising at least one polypeptide according to claim 2.

18. A fusion protein comprising a polypeptide according to claim 2 and a known lung tumor antigen.

19. A pharmaceutical composition comprising a fusion protein according to any one of claims 17-18 and a physiologically acceptable carrier.

20. A vaccine comprising a fusion protein according to any one of claims 17-18 and a non-specific immune response enhancer.

21. The vaccine of claim 20 wherein the non-specific immune response enhancer is an adjuvant.

22. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claim 19.

23. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of claim 20.

24. A method for detecting lung cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected

from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 the complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 under moderately stringent conditions; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting lung cancer in the patient.

25. The method of claim 24 wherein the binding agent is a monoclonal antibody.

26. The method of claim 25 wherein the binding agent is a polyclonal antibody.

27. A method for monitoring the progression of lung cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 the complements of said nucleotide sequences and sequences that hybridize to a nucleotide sequence of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 under moderately stringent conditions;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of lung cancer in the patient.

28. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 and 171; the complements of said nucleotide sequences; and sequences that hybridize to a nucleotide sequence of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30. 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168 or 171 under moderately stringent conditions.

29. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient a therapeutically effective amount of a monoclonal antibody according to claim 28.

30. The method of claim 29 wherein the monoclonal antibody is conjugated to a therapeutic agent.

31. A method for detecting lung cancer in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a lung protein or of a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 the complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-109, 111, 113, 115-151. 153, 154, 157, 158, 160, 162-164, 167, 168 or 171 under moderately stringent conditions; and

(c) detecting in the sample a polynucleotide sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting lung cancer.

32. The method of claim 31, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171.

33. A diagnostic kit comprising:

(a) one or more monoclonal antibodies of claim 28; and

(b) a detection reagent.

34. A diagnostic kit comprising:

(a) one or more monoclonal antibodies that bind to a polypeptide encoded by a polynucleotide molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 and 162-164 the complements of said sequences, and sequences that hybridize to a sequence of SEQ ID NO: 4, 5, 9, 14, 28, 31, 33, 50, 53, 56, 60, 70, 72, 75, 76, 79, 83, 85, 97-106, 115-124, 126, 130, 134-141, 143, 145-147 or 162-164 under moderately stringent conditions; and

(b) a detection reagent.

35. The kit of claims 33 or 34 wherein the monoclonal antibodies are immobilized on a solid support.

36. The kit of claim 35 wherein the solid support comprises nitrocellulose, latex or a plastic material.

37. The kit of claims 33 or 34 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

38. The kit of claim 37 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

39. The kit of claim 37 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

40. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 the complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164. 167, 168 or 171 under moderately stringent conditions.

41. A diagnostic kit of claim 40 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171.

42. A method for detecting lung cancer in a patient, comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171 the complements of said nucleotide sequences, and

sequences that hybridize to a sequence of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 or 171 under moderately stringent conditions; and

(c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe, thereby detecting lung cancer in the patient.

43. The method of claim 42 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from the group consisting of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171.

44. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a lung protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171; the complements of said nucleotide sequences; and sequences that hybridize to a sequence of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 or 171 under moderately stringent conditions.

45. The diagnostic kit of claim 44, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from the group consisting of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171.

46. A method for treating lung cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polypeptide of claim 2, such that T cells proliferate; and

(c) administering to the patient the proliferated T cells.

47. A method for treating lung cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polynucleotide of claim 1, such that T cells proliferate; and

(c) administering to the patient the proliferated T cells.

48. The method of any one of claims 46 and 47 wherein the step of incubating the T cells is repeated one or more times.

49. The method of any one of claims 46 and 47 wherein step (a) further comprises separating T cells from the peripheral blood cells, and the cells incubated in step (b) are the T cells.

50. The method of any one of claims 46 and 47 wherein step (a) further comprises separating CD4+ cells or CD8+ cells from the peripheral blood cells, and the cells proliferated in step (b) are CD4+ or CD8+ T cells.

51. The method of any one of claims 46 and 47 wherein step (b) further comprises cloning one or more T cells that proliferated in the presence of the polypeptide.

52. A composition for the treatment of lung cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of claim 2, in combination with a pharmaceutically acceptable carrier.

53. A composition for the treatment of lung cancer in a patient, comprising T cells proliferated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.

54. A method for treating lung cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polypeptide of claim 2;

(b) administering to the patient the incubated antigen presenting cells.

55. A method for treating lung cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polynucleotide of claim 1;

(b) administering to the patient the incubated antigen presenting cells.

56. The method of claims 54 or 55 wherein the antigen presenting cells are selected from the group consisting of dendritic cells and macrophage cells.

57. A composition for the treatment of lung cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of claim 2, in combination with a pharmaceutically acceptable carrier.

58. A composition for the treatment if lung cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.

SEQUENCE LISTING

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caatacacac tcatgaactc ctgatggaac aataacaggc ccaagcctgt ggtatgatgt 240
gcacacttgc tagactcaga aaaaatacta ctctcataaa tgggtgggag tattttgggt 300
gacaacctac tttgcttggc tgagtgaagg aatgatattc atatnttcat ttattccatg 360
gacatttagt tagtgctttt tatataccag gcatgatgct gagtgacact cttgtgtata 420
tntccaaatn ttngtncngt cgctgcacat atctgaaatc ctatattaag antttcccaa 480
natgangtcc ctggtttttc cacgccactt gatcngtcaa ngatctcacc tctgtntgtc 540
ctaaaaccnt ctnctnnang gttagacngg acctctcttc tcccttcccg aanaatnaag 600
tgtgngaaga nancncncn cccccctncn tncnncctng ccngctnnnc cncntgtngg 660

gggngccgcc cccgcggggg gacccccccn ttttcccc 698

<210> 6
<211> 740
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(740)
<223> n = A,T,C or G

<400> 6
actagtcaaa aatgctaaaa taatttggga gaaaatattt tttaagtagt gttatagttt 60
catgtttatc ttttattatg tnttgtgaag ttgtgtcttt tcactaatta cctatactat 120
gccaatattt ccttatatct atccataaca tttatactac atttgtaaga gaatatgcac 180
gtgaaactta acactttata aggtaaaaat gaggtttcca agatttaata atctgatcaa 240
gttcttgtta tttccaaata gaatggactt ggtctgttaa ggggctaagg gagaagaaga 300
agataaggtt aaaagttgtt aatgaccaaa cattctaaaa gaaatgcaaa aaaaaattta 360
ttttcaagcc ttcgaactat ttaaggaaag caaaatcatt tcctanatgc atatcatttg 420
tgaganttte tcantaatat cctgaatcat tcatttcagc tnaggcttca tgttgacccg 480
atatgtcatc tagggaaagt ctatttcatg gtccaaacct gttgccatag ttggtnaggc 540
tttcctttaa ntgtgaanta ttnacangaa attttctctt tnanagttct tnatagggtt 600
aggggtgtgg gaaaagcttc taacaatctg tagtgttncg tgttatctgt ncagaaccan 660
aatnacggat cgnangaagg actgggtcta tttacangaa cgaatnatct ngttnnntgt 720
gtnnncaact ccngggagcc 740

<210> 7
<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 7
gctggggagc tcggcatggc ggtccccgct gcagccatgg ggccctcggc gttgggccag 60
agcggccccg gctcgatggc cccgtggtgc tcagtgagca gcggcccgtc gcgctacgtg 120
cttgggatgc aggagctgtt ccggggccac agcaagaccg cgagttcctg gcgcacagcg 180
ccaaggtgca ctcggtggcc tggagttgcg acgggcgtcg cctacctcgg ggtcttcgac 240
aagacgccac gtcttcttgc tgganaanga ccgttggtca aagaaaacaa ttatcgggga 300
catggggata gtgtggacca ctttgttggc atccaagtaa tcctgaccta tttgttacgg 360
cgtctggaga taaaaccatt cgcatctggg atgtgaggac tacaaaatgc attgccactg 420
tgaacactaa aggggagaac attaatatct gctggantcc tgatgggcan accattgctg 480
tagcnacaag gatgatgtgg tgacttttatt gatgccaaga aaccccgttc caaagcaaaa 540
aaacanttcc aanttcgaag tcaccnaaat ctcctggaac aatgaacatn aatatnttct 600
tcctgacaat ggnccttggg tgtntcacat cctcagctnc cccaaaactg aancctgtnc 660
natccacccc 670

<210> 8
<211> 689
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(689)
<223> n = A,T,C or G

<400> 8
actagtatct aggaatgaac agtaaaagag gagcagttgg ctacttgatt acaacagagt 60
aaatgaagta ctggatttgg gaaaacctgg ttttattaga acatatggaa tgaaagccta 120
cacctagcat tgcctactta gccccctgaa ttaacagagc ccaattgaga caaacccctg 180
gcaacaggaa attcaaggga gaaaaagtaa gcaacttggg ctaggatgag ctgactccct 240
tagagcaaag ganagacagc ccccattacc aaataccatt tttgcctggg gcttgtgcag 300
ctggcagtgt tcctgccnca gcatggcacc ttatngtttt gatagcaact tcgttgaatt 360
ttcaccaact tattacttga aattataata tagcctgtcc gtttgctgtn tccaggctgt 420
gatatatntt cctagtggtt tgactttnaa aataaatnag gtttantttt ctcccccnnn 480
cnntnctncc nntcnctcnn cnntcccccc cnctcngtcc tccnnnnnttn ggggggccn 540
ccccccnggn ggaccccccc ttggtccctt agtggaggtt natggccccc ggnnttatcc 600
nggccntann tttccccgtn nnaaatgntt ccccctccca ntcccnccac ctcaancegg 660
aagcctaagt ttntaccctg ggggtcccc 689

<210> 9
<211> 674
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(674)
<223> n = A,T,C or G

<400> 9
gtccactctc ctttgagtgt actgtcttac tgtgcactct gtttttcaac tttctagata 60
taaaaaatgc ttgttctata gtggagtaag agctcacaca cccaaggcag caagataact 120
gaaaaaagcg aggctttttt gccaccttgg taaaggccag ttcactgcta tagaactgct 180
ataagcctga agggaagtag ctatgagact ttccattttt cttagttctc ccaataggct 240
ccttcatgga aaaaggcttc ctgtaataat tttcacctaa tgaattagca gtgtgattat 300
ttctgaaata agagacaaat tgggccgcag agtcttcctg tgatttaaaa taaacaaccc 360
aaagttttgt ttggtcttca ccaaaggaca tactctaggg ggtatgttgt tgaagacatt 420
caaaaacatt agctgttctg tcttttcaatt tcaagttatt ttggagactg cctccatgtg 480
agttaattac tttgctctgg aactagcatt attgtcatta tcatcacatt ctgtcatcat 540
catctgaata atattgtgga tttccccctc tgcttgcatc ttcttttgac tcctctggga 600
anaaatgtca aaaaaaaagg tcgatctact cngcaaggnc catctaatca ctgcgctgga 660
aggacccnct gccc 674

<210> 10
<211> 346
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(346)
<223> n = A,T,C or G

<400> 10

<221> misc_feature
<222> (1)...(694)
<223> n = A,T,C or G

<400> 13
cactagtcac tcattagcgt tttcaatagg gctcttaagt ccagtagatt acgggtagtc 60
agttgacgaa gatctggttt acaagaacta attaaatgtt tcattgcatt tttgtaagaa 120
cagaataatt ttataaaatg tttgtagttt ataattgccg aaaataattt aaagacactt 180
tttctctgtg tgtgcaaatg tgtgtttgtg atccattttt ttttttttt taggacacct 240
gtttactagc tagctttaca atatgccaaa aaaggatttc tccctgaccc catccgtggt 300
tcaccctctt ttccccccat gctttttgcc ctagtttata acaaaggaat gatgatgatt 360
taaaaagtag ttctgtatct tcagtatctt ggtcttccag aacccctctgg ttgggaaggg 420
gatcattttt tactggtcat ttccctttgg agtgtactac tttaacagat ggaaagaact 480
cattggccat ggaaacagcc gangtgttgg gagccagcag tgcatggcac cgtccggcat 540
ctggcntgat tggtctggct gccgtcattg tcagcacagt gccatgggac atggggaana 600
ctgactgcac ngccaatggt tttcatgaag aatacngcat ncncngtgat cacgtnancc 660
angacgctat gggggncana gggccanttg cttc 694

<210> 14
<211> 679
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(679)
<223> n = A,T,C or G

<400> 14
cagccgcctg catctgtatc cagcgccang tcccgccagt cccagctgcg cgcgcccccc 60
agtcccgnac ccgttcggcc cangctnagt tagncctcac catnccggtc aaaggangca 120
ccaagtgcat caaatacctg cngtncggat ntaaattcat cttctggctt gccgggattg 180
ctgtccntgc cattggacta nggctccgat ncgactctca gaccanganc atctttcganc 240
naganactaa tnatnattnt tccagcttct acacaggagt ctatattctg atcggatccg 300
gcncccctcnt gatgctggtg ggcttcctga gctgctgcgg ggctgtgcaa gagtcccant 360
gcatgctggg actgttcttc ggcttcntct tggtgatatn cgccattgaa atacctgcgg 420
ccatctgggg atattccact ncgatnatgt gattaaggaa ntccacggag ttttacaagg 480
acacgtacaa cnacctgaaa accnnggatg anccccaccg ggaancnctg aangccatcc 540
actatgcgtt gaactgcaat ggtttggctg gggnccttga acaatttaat cncatacatc 600
tggccccann aaaggacntn ctcganncct tcnccgtgna attcngttct gatnccatca 660
cagaagtctc gaacaatcc 679

<210> 15
<211> 695
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(695)
<223> n = A,T,C or G

<400> 15
actagtggat aaaggccagg gatgctgctc aacctcctac catgtacagg gacgtcccct 60
cattacaact accaatccg aagtgtcaac tgtgtcagga ctaanaaacc ctggtcctga 120

actagtctgc tgatagaaag cactatacat cctattgttt ctttctttcc aaaatcagcc 60
ttctgtctgt aacaaaaatg tactttatag agatggagga aaaggtctaa tactacatag 120
ccttaagtgt ttctgtcatt gttcaagtgt attttctgta acagaaacat atttggaatg 180
ttttttcttt ccccttataa attgtaattc ctgaaatact gctgctttaa aaagtcccac 240
tgtcagatta tattatctaa caattgaata ttgtaaatat acttgtctta cctctcaata 300
aaagggtact tttctattan nnagnngnnn gnnnnataaa anaaaa 346

<210> 11
<211> 602
<212> DNA
<213> Homo sapien

<400> 11
actagtaaaa agcagcattg ccaaataatc cctaattttc cactaaaaat ataatgaaat 60
gatgttaagc tttttgaaaa gtttaggtta aacctactgt tgttagatta atgtatttgt 120
tgcttcccct tatctggaat gtggcattag cttttttatt ttaaccctct ttaattctta 180
ttcaattcca tgacttaagg ttggagagct aaacactggg atttttggat aacagactga 240
cagttttgca taattataat cggcattgta catagaaagg atatggctac cttttgttaa 300
atctgcactt tctaaatatc aaaaaaggga aatgaagtta taaatcaatt tttgtataat 360
ctgtttgaaa catgagtttt atttgcttaa tattagggct ttgccccttt tctgtaagtc 420
tcttgggatc ctgtgtagaa ctgttctcat taaacaccaa acagttaagt ccattctctg 480
gtactagcta caaattcggt ttcatatttct acttaacaat ttaaataaac tgaaatattt 540
ctagatggtc tacttctgtt catataaaaa caaaacttga tttccaaaaa aaaaaaaaaa 600
aa 602

<210> 12
<211> 685
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(685)
<223> n = A,T,C or G

<400> 12
actagtcctg tgaaagtaca actgaaggca gaaagtgtta ggattttgca tctaatgttc 60
attatcatgg tattgatgga cctaagaaaa taaaaattag actaagcccc caaataagct 120
gcatgcattt gtaacatgat tagtagattt gaatatatag atgtagtatn ttgggtatct 180
aggtgtttta tcattatgta aaggaattaa agtaaaggac tttgtagttg tttttattaa 240
atatgcatat agtagagtgc aaaaatatag caaaaatana aactaaaggt agaaaagcat 300
tttagatatg ccttaatnta nnaactgtgc caggtggccc tcggaataga tgccaggcag 360
agaccagtgc ctgggtggtg cctccccttg tctgcccccc tgaagaactt ccctcacgtg 420
angtagtgcc ctcgtaggtg tcacgtggan tantgggganc aggccgnncn gtnanaagaa 480
ancanngtga nagtttcncc gtngangcng aactgtccct gngccnnnac gctcccanaa 540
cntntccaat ngacaatcga gtttccnnnc tccngnaacc tngccgnnnn cnngcccnnc 600
cantntgnta accccgcgcc cggatcgctc tcnnntcgtt ctcncncnaa ngggnttttn 660
cnnccgccgt cncnnccccg cnncc 685

<210> 13
<211> 694
<212> DNA
<213> Homo sapien

<220>

ttaaaaaagg gcctgaaaaa aggggagcca caaatctgtc tgcttcctca cnttantcnt 180
tggcaaatna gcattctgtc tcnttggctg cngcctcanc ncaaaaaanc ngaactcnat 240
cnggcccagg aatacatctc ncaatnaacn aaattganca aggcnntggg aaatgccnga 300
tgggattatc ntccgcttgt tgancttcta agtttcnttc ccttcattcn accctgccag 360
ccnagttctg ttagaaaaat gccngaattc naacnccggt tttcntactc ngaatttaga 420
tctncanaaa cttcctggcc acnattcnaa ttnanggnca cgnacanatn ccttccatna 480
ancncaccce acntttgana gccangacaa tgactgcntn aantgaaggc ntgaaggaan 540
aactttgaaa ggaaaaaaaa ctttgtttcc ggcccccttcc aacncttctg tgttnancac 600
tgccttctng naaccctgga agcccngnga cagtgttaca tgttgttcta nnaaacngac 660
ncttnaatnt cnatcttccc nanaacgatt ncncc 695

<210> 16
<211> 669
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(669)
<223> n = A,T,C or G

<400> 16
cgccgaagca gcagcgcagg ttgtccccgt ttcccctccc ccttcccttc tccggttgcc 60
ttcccgggcc ccttacactc cacagtcccg gtcccgccat gtcccagaaa caagaagaag 120
agaacccctgc ggaggagacc ggcgaggaga agcaggacac gcaggagaaa gaaggtattc 180
tgcctgagag agctgaagag gcaaagctaa aggccaaata cccaagccta ggacaaaagc 240
ctggaggctc cgacttcctc atgaagagac tccagaaagg gcaaaagtac tttgactcng 300
gagactacaa catggccaaa gccaacatga agaataagca gctgccaagt gcangaccag 360
acaagaaccc ggtgactggt gatcacatcc ccacccccaca ggatctgccc agagaaagtc 420
ctcgctcgtc accagcaagc ttgcgggtgg ccaagttgaa tgatgctgcc ggggctctgc 480
canatctgag acgcttcccc ccctgcccca cccgggtcct gtgctggctc ctgccccttcc 540
tgcttttgca gccangggtc aggaagtggc ncnggtngtg gctggaaagc aaaaccccttt 600
cctgttggtg tcccacccat ggagcccctg gggcgagccc angaacttga ncccttttgt 660
tntcttncc 669

<210> 17
<211> 697
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(697)
<223> n = A,T,C or G

<400> 17
gcaagatatg gacaactaag tgagaaggta atnctctact gctctagntn ctccnggcnn 60
gacgcgctga ggagannnac gctggcccan ctgccggcca cacacgggga tcntggtnat 120
gcctgcccan gggancccca ncnctcggan cccatntcac acccgnnccn tncgcccacn 180
ncctggctcn cncngcccng nccagcttnc gncccccctcc gccnnnnctcn ttnncntctc 240
cncncccctcc ncnacnacct cctacccncg gctcccctccc cagccccccc ccgcaancct 300
ccacnacncc ntcnncncga ancncencte gcnctcngcc ccngccccct gccccccgcc 360
cncnacnncg cgntcccccg cgcncgcngc ctcncccccct cccacnacag ncncaccegc 420
agncacgcnc tccgcccnct gacgcccnnn cccgccgcgc tcaccttcat ggnccnacng 480
ccccgctcnc ncccctgcnc gccgncnngg cgccccgccc cnncegngtn ccncncgnng 540

ccccngcngn angcngtgcg cnncangncc gngccgnncn ncaccctccg nccnccgccc 600
cgcccgctgg gggctcccgc cncgcggntc antccccncc cntncgccca ctntccgntc 660
cnncnctcnc gctcngcgcn cgcccnccnc ccccccc 697

<210> 18
<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 18
ctcgtgtgaa gggtgcagta cctaagccgg agcggggtag aggcgggccg gcaccccctt 60
ctgacctcca gtgccgccgg cctcaagatc agacatggcc cagaacttga acgacttggc 120
gggacggctg cccgccgggc cccggggcat gggcacggcc ctgaagctgt tgctgggggc 180
cggcgccgtg gcctacggtg tgcgcgaatc tgtgttcacc gtggaaggcg ggcncagagc 240
catcttcttc aatcggatcg gtggagtgca caggacacta tcctgggccg anggccttca 300
cttcaggatc cttggttcca gtaccccanc atctatgaca ttcgggccag acctcgaaaa 360
aatcrcctcc ctacaggctc caaagaccta cagatggtga atatctcccc gcgagtgttg 420
tctcgaccaa tgcttcangaa cttcctaaca tgttccancg cctaagggct ggactacnaa 480
gaacgantgt tgccgtccat tgtcacgaag tgctcaagaa tttnggtggc caagttcaat 540
gncctcacnn ctgatcnccc agcggggcca agttanccct ggttgatccc cgggganctg 600
acnnaaaagg gccaaggact tcccctcatc ctggataatg tggccntcac aaagcttcaac 660
tttanccacc 670

<210> 19
<211> 606
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(606)
<223> n = A,T,C or G

<400> 19
actagtgcca acctcagctc ccaggccagt tctctgaatg tcgaggagtt ccaggatctc 60
tggcctcagt tgtccttggt tattgatggg ggacaaattg gggatggcca gagccccgag 120
tgtcgccttg gctcaactgt ggttgatttg tctgtgcccg gaaagtttgg catcattcgt 180
ccaggctgtg ccctggaaag tactacagcc atcctccaac agaagtacgg actgctcccc 240
tcacatgcgt cctacctgtg aaactctggg aagcaggaag gcccaagacc tggtgctgga 300
tactatgtgt ctgtccactg acgactgtca aggcctcatt tgcagaggcc accggagcta 360
gggcactagc ctgactttta aggcagtgtg tcttttctgag cactgtagac caagcccttg 420
gagctgctgg tttagccttg cacctgggga aaggatgtat ttatttgtat tttcatatat 480
cagccaaaag ctgaatggaa aagttnagaa cattcctagg tggccttatt ctaataagtt 540
tcttttgtct gttttgtttt tcaattgaaa agttattaaa taacagattt agaatctagt 600
gagacc 606

<210> 20
<211> 449
<212> DNA
<213> Homo sapien

<400> 20
actagtaaac aacagcagca gaaacatcag tatcagcagc gtcgccagca ggagaatatg 60
cagcgccaga gccgaggaga acccccgctc cctgaggagg acctgtccaa actcttcaaa 120
ccaccacagc cgcctgccag gatggactcg ctgctcattg caggccagat aaacacttac 180
tgccagaaca tcaaggagtt cactgcccaa aacttaggca agctcttcat ggcccaggct 240
cttcaagaat acaacaacta agaaaaggaa gtttccagaa aagaagttaa catgaactct 300
tgaagtcaca ccagggcaac tcttggaaga aatatatttg catattgaaa agcacagagg 360
atttctttag tgtcattgcc gattttggct ataacagtgt ctttctagcc ataataaaat 420
aaaacaaaat cttgactgct tgctcaaaa 449

<210> 21
<211> 409
<212> DNA
<213> Homo sapien

<400> 21
tatcaatcaa ctggtgaata attaaacaat gtgtggtgtg atcatacaaa gggtaccact 60
caatgataaa aggaacaagc tgcctatatg tggaacaaca tggatgcatt tcagaaactt 120
tatgttgagt gaaagaacaa acacggagaa catactatgt ggttctcttt atgtaacatt 180
acagaaataa aaacagaggc aaccaccttt gaggcagtat ggagtgagat agactggaaa 240
aaggaaggaa ggaaactcta cgctgatgga aatgtctgtg tcttcattgg gtggtagtta 300
tgtggggata tacatttgtc aaaatttatt gaactatata ctaaagaact ctgcatttta 360
ttgggatgta aataatacct caattaaaaa gacaaaaaaa aaaaaaaaa 409

<210> 22
<211> 649
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(649)
<223> n = A,T,C or G

<400> 22
acaattttca ttatcttaag cacattgtac atttctacag aacctgtgat tattctcgca 60
tgataaggat ggtacttgca tatggtgaat tactactgtt gacagtttcc gcagaaatcc 120
tatttcagtg gaccaacatt gtggcatggc agcaaatgcc aacattttgt ggaatagcag 180
caaatctaca agagaccctg gttggttttt cgttttgttt tctttgtttt ttcccccttc 240
tcctgaatca gcagggatgg aangagggta gggaagttat gaattactcc ttccagtagt 300
agctctgaag tgtcacattt aatatcagtt ttttttaaac atgattctag ttnaatgtag 360
aagagagaag aaagaggaag tgttcacttt tttaatacac tgatttagaa atttgatgtc 420
ttatatcagt agttctgagg tattgatagc ttgctttatt tctgccttta cgttgacagt 480
gttgaagcag ggtgaataac taggggcata tatatttttt ttttttgtaa gctgtttcat 540
gatgttttct ttggaatttc cggataagtt caggaaaaca tctgcatgtt gttatctagt 600
ctgaagttcn tatccatctc attacaacaa aaacncccag aacggnttg 649

<210> 23
<211> 669
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(669)
<223> n = A,T,C or G

<400> 23
actagtgccg tactggctga aatccctgca ggaccaggaa gagaaccagt tcagactttg 60
tactctcagt caccagctct ggaattagat aaattccttg aagatgtcag gaatgggatc 120
tatcctctga cagcctttgg gctgcctcgg ccccagcagc cacagcagga ggaggtgaca 180
tcacctgtcg tgccccccta tgtcaagact ccgacacctg aaccagctga ggtggagact 240
cgcaaggtgg tgctgatgca gtgcaacatt gagtcggtgg aggagggagt caaacaccac 300
ctgacacttc tgctgaagtt ggaggacaaa ctgaaccggc acctgagctg tgacctgatg 360
ccaaatgaga atatccccga gttggcggct gagctggtgc agctgggctt cattagtgag 420
gctgaccaga gccggttgac ttctctgcta gaagagactt gaacaagttc aattttgcca 480
ggaacagtac cctcaactca gccgctgtca ccgtctcctc ttagagctca ctcgggccag 540
gccctgatct gcgctgtggc tgtcctggac gtgctgcacc ctctgtcctt ccccccagtc 600
agtattacct gtgaagccct tccctccttt attattcagg anggctgggg gggctccttg 660
nttctaacc 669

<210> 24
<211> 442
<212> DNA
<213> Homo sapien

<400> 24
actagtacca tcttgacaga ggatacatgc tcccaaaacg tttgttacca cacttaaaaa 60
tcactgccat cattaagcat cagtttcaaa attatagcca ttcatgattt actttttcca 120
gatgactatc attattctag tcctttgaat ttgtaagggg aaaaaaaaca aaaacaaaaa 180
cttacgatgc acttttctcc agcacatcag atttcaaatt gaaaattaaa gacatgctat 240
ggtaatgcac ttgctagtac tacacacttt ggtacaacaa aaaacagagg caagaaacaa 300
cggaaagaga aaagccttcc tttgttggcc cttaaactga gtcaagatct gaaatgtaga 360
gatgatctct gacgatacct gtatgttctt attgtgtaaa taaaattgct ggtatgaaat 420
gacctaaaaa aaaaaaaaga aa 442

<210> 25
<211> 656
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(656)
<223> n = A,T,C or G

<400> 25
tgcaagtacc acacactgtt tgaattttgc acaaaaagtg actgtaggat caggtgatag 60
ccccggaatg tacagtgtct tggtgcacca agatgccttc taaaggctga catacattgg 120
accctaatgg ggcagagagt atagccctag cccagtggtg acatgaccac tccctttggg 180
aggcctgagg tagaggggag tggtatgtgt tttctcagtg gaagcagcac atgagtgggt 240
gacaggatgt tagataaagg ctctagttag ggtgtcattg tcatttgaga gactgacaca 300
ctcctagcag ctggtaaagg ggtgctggan gccatggagg anctctagaa acattagcat 360
gggctgatct gattactttc tggcatcccg ctcactttta tgggaagtct tattagangg 420
atgggacagt tttccatatc cttgctgtgg agctctggaa cactctctaa atttcccttt 480
attaaaaatc actgccctaa ctacacttcc tccttgaagg aatagaaatg gaacttttct 540
tgacatantt cttggcatgg ggagccagcc acaaatgana atctgaacgt gtccaggttt 600
ctcctganac tcatctacat agaattggtt aaaccctccc ttggaataag gaaaaa 656

<210> 26
<211> 434
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(434)
<223> n = A,T,C or G

<400> 26
actagttcag actgccacgc caaccccaga aaatacccca catgccagaa aagtgaagtc 60
ctaggtgttt ccatctatgt ttcaatctgt ccatctacca ggcctcgcga taaaaacaaa 120
acaaaaaaac gctgccaggt tttagaagca gttctggtct caaaaccatc aggatcctgc 180
caccagggtt cttttgaaat agtaccacat gtaaaaggga atttggcttt cacttcatct 240
aataactgaa ttgtcaggct ttgattgata attgtagaaa taagtagcct tctgttgtgg 300
gaataagtta taatcagtat tcatctcttt gtttttttgtc actcttttct ctctaattgt 360
gtcatttgta ctgtttgaaa aatattttctt ctatnaaatt aaactaacct gccttaaaaa 420
aaaaaaaaaa aaaa 434

<210> 27
<211> 654
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(654)
<223> n = A,T,C or G

<400> 27
actagtccaa cacagtcaga aacattgttt tgaatcctct gtaaaccaag gcattaatct 60
taataaacca ggatccattt aggtaccact tgatataaaa aggatatcca taatgaatat 120
tttatactgc atcctttaca ttagccacta aatacgttat tgcttgatga agacctttca 180
cagaatccta tggattgcag catttcactt ggctacttca tacccatgcc ttaaagaggg 240
gcagtttctc aaaagcagaa acatgccgcc agttctcaag ttttcctcct aactccattt 300
gaatgtaagg gcagctggcc cccaatgtgg ggaggtccga acatttttctg aattcccatt 360
ttcttgttcg cggctaaatg acagtttctg tcattactta gattccgatc tttcccaaag 420
gtgttgattt acaaagaggc cagctaatag cagaaatcat gaccctgaaa gagagatgaa 480
attcaagctg tgagccaggc agganctcag tatggcaaag gtcttgagaa tcngccattt 540
ggtacaaaaa aaatttttaaa gcntttatgt tataccatgg aaccatagaa anggcaaggg 600
aattgttaag aanaatttta agtgtccaga cccanaanga aaaaaaaaaa aaaa 654

<210> 28
<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 28
cgtgtgcaca tactgggagg atttccacag ctgcacggtc acagcccctta cggattgcca 60

ggaaggggcg aaagatatgt gggataaact gagaaaagaa nccaaaaacc tcaacatcca 120
aggcagctta ttcgaactct gcggcagcgg caacggggcg gcggggtccc tgctcccggc 180
gttcccggtg ctcctggtgt ctctctcggc agctttagcg acctgncttt cctttctgagc 240
gtggggccag ctcccccccgc ggcgcccacc cacnctcact ccatgctccc ggaaatcgag 300
aggaagatca ttagttcttt ggggacgttn gtgattctct gtgatgctga aaaacactca 360
tatagggaat gtgggaaatc ctganctctt tnttatntcg tntgatttct tgtgttttat 420
ttgccaaaat gttaccaatc agtgaccaac cnagcacagc caaaaatcgg acntcngctt 480
tagtccgtct tcacacacag aataagaaaa cggcaaaccc accccacttt tnantttnat 540
tattactaan ttttttctgt tgggcaaaag aatctcagga acngccctgg ggccnccgta 600
ctanagttaa ccnagctagt tncatgaaaa atgatgggct ccncctcaat gggaaagcca 660
agaaaaagnc 670

<210> 29
<211> 551
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(551)
<223> n = A,T,C or G

<400> 29
actagtcctc cacagcctgt gaatcccact agacctttca agcatagtga gcggagaaga 60
agatctcagc gtttagccac cttacccatg cctgatgatt ctgtagaaaa ggtttcttct 120
ccctctccag ccactgatgg gaaagtattc tccatcagtt ctcaaaatca gcaagcatct 180
tcagtaccag aggtgcctga tgttgcacac ttgccacttg agaagctggg accctgtctc 240
cctcttgact taagtcgtgg ttcagaagtt acagcaccgg tagcctcaga ttcctcttac 300
cgtaatgaat gtcccagggc agaaaaagag gatacncaga tgcttccaaa tcctttcttc 360
aaagcaatag ctgatgggaa gaggagctcc agcagcagca ggaatatcga aaacagaaaa 420
aaaagtgaaa ttgggaagac aaaagctcaa cagcatttgg taaggagaaa aganaagatg 480
aggaaggaag agagaagaga gacnaagatc nctacggacc gnnncggaag aagaagaagn 540
aaaaaanaaa a 551

<210> 30
<211> 684
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(684)
<223> n = A,T,C or G

<400> 30
actagttcta tctggaaaaa gcccgggttg gaagaagctg tggagagtgc gtgtgcaatg 60
cgagactcat ttcttggaag catcctggc aaaaatgcag ctgagtacaa ggttatcact 120
gtgatagaac ctggactgct ttttgagata atagagatgc tgcagtctga agagacttcc 180
agcaccttc agttgaatga attaatgatg gcttctgagt caactttact ggctcaggaa 240
ccacgagaga tgactgcaga tgtaatcgag cttaaaggga aattcctcat caacttagaa 300
ggtggtgata ttcgtgaaga gtcttcctat aaagtaattg tcatgccgac tacgaaagaa 360
aaatgccccc gttgttggaa gtatacagcg ggagtcttca gatacactgt gtcctcgatg 420
tgcagaagtt gtcagtggga aaatagtatt aacagctcac tcgagcaaga accctcctga 480
cagtactggg ctagaagttt ggatggatta tttacaatat aggaaagaaa gccaagaatt 540
aggtnatgag tggatgagta aatggtggan gatggggaat tcaaatcaga attatggaag 600

aagttnttcc tgttactata gaaaggaatt atgtttattt acatgcagaa aatatanatg 660
tgtggtgtgt accgtggatg gaan 684

<210> 31
<211> 654
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(654)
<223> n = A,T,C or G

<400> 31
gcgcagaaaa ggaaccaata tttcagaaac aagcttaata ggaacagctg cctgtacatc 60
aacatcttct cagaatgacc cagaagttat catcgtggga gctggcgtgc ttggctctgc 120
tttggcagct gtgctttcca gagatggaag aaaggtgaca gtcattgaga gagacttaaa 180
agagcctgac agaatagttg gagaattcct gcagccgggt ggttatcatg ttctcaaaga 240
ccttggtctt ggagatacag tggaaggtct tgatgcccag gttgtaaatg gttacatgat 300
tcatgatcag ggaaagcaaa tcagangttc agattcctta ccctctgtca gaaaacaatc 360
aagtgcagag tggaagagct ttccatcacg gaagattcat catgagtctc cggaaagcag 420
ctatggcaga gcccaatgca aagtttattg aaggtgttgt gttacagtta ttagaggaag 480
atgatgttgt gatgggagtt cagtacaagg ataaagagac tgggagatat caaggaactc 540
catgctccac tgactgttgt tgcagatggg cttttctcca anttcaggaa aagcctggtc 600
tcaataaagt ttctgtatca ctcatttggt tggcttctta tgaagaatgc nccc 654

<210> 32
<211> 673
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(673)
<223> n = A,T,C or G

<400> 32
actagtgaag aaaaagaaat tctgatacgg gacaaaaatg ctcttcaaaa catcattctt 60
tatcacctga caccaggagt tttcattgga aaaggatttg aacctggtgt tactaacatt 120
ttaaagacca cacaaggaag caaaatcttt ctgaaagaag taaatgatac acttctggtg 180
aatgaattga aatcaaaaga atctgacatc atgacaacaa atggtgtaat tcatgttgta 240
gataaactcc tctatccagc agacacacct gttggaaatg atcaactgct ggaaatactt 300
aataaattaa tcaaatacat ccaaattaag tttgttcgtg gtagcacctt caaagaaatc 360
cccgtgactg tctatnagcc aattattaaa aaatacacca aaatcattga tgggagtgcc 420
tgtgggaaat aactgaaaaa gagaccgaga agaacgaatc attacaggtc ctgaaataaa 480
atacctagga tttctactgg aggtggagaa acagaagaac tctgaagaaa ttgttacaag 540
aagangtccc aaggtcacca aattcattga aggtggtgat ggtctttatt tgaagatgaa 600
gaaattaaaa gacgcttcag ggagacnccc catgaaggaa ttgccagcca caaaaaaatt 660
cagggattag aaa 673

<210> 33
<211> 673
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(673)
<223> n = A,T,C or G

<400> 33
actagttatt tactttcctc cgcttcagaa ggtttttcag actgagagcc taagcatact 60
ggatctgttg tttcttttgg gtctcacctc atcagtgtgc atagtggcag aaattataaa 120
gaaggttgaa aggagcaggg aaaagatcca gaagcatgtt agttcgacat catcatcttt 180
tcttgaagta tgatgcatat tgcattattt tatttgcaaa ctaggaattg cagtctgagg 240
atcatttaga agggcaagtt caagaggata tgaagatttg agaacttttt aactattcat 300
tgactaaaaa tgaacattaa tgttnaagac ttaagacttt aacctgctgg cagtcccaaa 360
tgaaattatg caactttgat atcatattcc ttgatttaaa ttgggctttt gtgattgant 420
gaaactttat aaagcatatg gtcagttatt tnattaaaaa ggcaaaacct gaaccaccct 480
ctgcacttaa agaagtctaa cagtacaaat acctatctat cttagatgga tntatttntt 540
tntattttta aatattgtac tatttatggt nggtggggct ttcttactaa tacacaaatn 600
aatttatcat ttcaanggca ttctatttgg gtttagaagt tgattccaag nantgcatat 660
ttcgctactg tnt 673

<210> 34
<211> 684
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(684)
<223> n = A,T,C or G

<400> 34
actagtttat tcaagaaaag aacttactga ttcctctgtt cctaaagcaa gagtggcagg 60
tgatcagggc tggtgtagca tccggttcct ttagtgcagc taactgcatt tgtcactgat 120
gaccaaggag gaaatcacta agacatttga gaagcagtgg tatgaacgtt cttggacaag 180
ccacagttct gagccttaac cctgtagttt gcacacaaga acgagctcca cctcccctta 240
ttcaggagga atctgtgcgg atagattggc tggacttttc aatggttctg ggttgcaagt 300
gggcactgtt atggctgggt atggagcgga cagccccagg aatcagagcc tcagcccggc 360
tgcctggttg gaaggtacag gtgttcagca ccttcggaaa aagggcataa agtngtgggg 420
gacaattctc agtccaagaa gaatgcattg accattgctg gctatttgct tncctagtan 480
gaattggatn catttttgac cangatnntt ctnctatgct ttnttgcaat gaaatcaaat 540
cccgcattat ctacaagtgg tatgaagtcc tgcnnccccc agagaggctg ttcaggcnat 600
gtcttccaag ggcagggtgg gttacaccat ttacctcccc ctctcccccc agattatgna 660
cncagaagga atttntttcc tccc 684

<210> 35
<211> 614
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(614)
<223> n = A,T,C or G

<400> 35
actagtccaa cgcgttngcn aatattcccc tggtagccta cttccttacc cccgaatatt 60

ggtaagatcg agcaatggct tcaggacatg ggttctcttc tcctgtgatc attcaagtgc 120
tcactgcatg aagactggct tgtctcagtg tntcaacctc accagggctg tctcttggtc 180
cacacctcgc tcccctgttag tgccgtatga cagcccccat canatgacct tggccaagtc 240
acggtttctc tgtggtcaat gttggtnggc tgattggtgg aaagtanggt ggaccaaagg 300
aagncncgtg agcagncanc nccagttctg caccagcagc gcctccgtcc tactngggtg 360
ttccngtttc tcctggcccc gngtgggcta nggcctgatt cgggaanatg cctttgcang 420
gaaggganga taantgggat ctaccaattg attctggcaa aacnatntct aagattnttn 480
tgctttatgt ggganacana tctanctctc atttnntgct gnanatnaca ccctactcgt 540
gntcgancnc gtcttcgatt ttcgganaca cnccantnaa tactggcgtt ctgttgttaa 600
aaaaaaaaaa aaaa 614

<210> 36
<211> 686
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(686)
<223> n = A,T,C or G

<400> 36
gtggctggcc cggttctccg cttctcccca tcccctactt tcctcccctc ctcccctttcc 60
ctcctcgtc gactgttgct tgctggtcgc agactcccctg acccctcccc caccccctccc 120
taacctcggt gccaccggat tgcccttctt ttcctgttgc ccagcccagc cctagtgtca 180
gggcgggggc ctggagcagc ccgaggcact gcagcagaag ananaaaaga cacgacnaac 240
ctcagctcgc cagtccggtc gctngcttcc cgccgcatgg caatnagaca gacgccgctc 300
acctgctctg ggcacacgcg acccgtggtt gatttggcct tcagtggcat cacccttatg 360
ggtatttctt aatcagcgct tgcaaagatg gttaacctat gctacgccag ggagatacag 420
gagactggat tggaacattt ttggggtcta aaggtctgtt tggggtgcaa cactgaataa 480
ggatgccacc aaagcagcta cagcagctgc agatttcaca gcccaagtgt gggatgctgt 540
ctcagganat naattgataa cctggctcat aacacattgt caagaatgtg gatttcccca 600
ggatattatt atttgtttac cgggggganag gataactgtt tcncntattt taattgaaca 660
aactnaaaca aaanctaagg aaatcc 686

<210> 37
<211> 681
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(681)
<223> n = A,T,C or G

<400> 37
gagacanacn naacgtcang agaanaaaag angcatggaa cacaanccag gcncgatggc 60
caccttccca ccagcancca gcgccccccca gcngcccccca ngnccggang accangactc 120
cancctgnat caatctganc tctattcctg gcccatncct acctcggagg tggangccgn 180
aaaggtcgca cnnncagaga agctgctgcc ancaccance gccccnnccc tgncgggctn 240
nataggaaac tggtgaccnn gctgcanaat tcatacagga gcacgcgang ggcacnnnct 300
cacactgagt tnnngatgan gcctnaccan ggacctnccc cagcnnattg annacnggac 360
tgcggaggaa ggaagacccc gnacnggatc ctggccggcn tgccaccccc ccaccccctag 420
gattatnccc cttgactgag tctctgaggg gctaccccgaa cccgcctcca ttcccctacca 480
natnntgctc natcgggact gacangctgg ggatnggagg ggctatcccc cancatcccc 540

tnanaccaac agcnacngan natnggggct ccccngggtc ggngcaacnc tcctncaccc 600
cggcgcnggc cttcggtgnt gtcctccntc aacnaattcc naaanggcgg gccccccngt 660
ggactcctcn ttgttccctc c 681

<210> 38
<211> 687
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(687)
<223> n = A,T,C or G

<400> 38
canaaaaaaa aaaacatggc cgaaaccagn aagctgcgcg atggcgccac ggcccctctt 60
ctcccggcct gtgtccggaa ggtttccctc cgaggcgccc cggctcccgc aagcggagga 120
gagggcggga cntgccgggg ccggagctca naggccctgg ggccgctctg ctctcccgcc 180
atcgcaaggg cggcgctaac ctnaggcctc cccgcaaagg tccccnangc ggnggcggcg 240
gggggctgtg anaaccgcaa aaanaacgct gggcgcgcng cgaacccgtc cacccccgcg 300
aaggananac ttccacagan gcagcgtttc cacagcccan agccacnttt ctagggtgat 360
gcaccccagt aagttcctgn cggggaagct caccgctgtc aaaaaaancc ttcgctccac 420
cggcgcacna aggggangan ggcangangc tgccgccgc acaggtcatc tgatcacgtc 480
gcccgcccta ntctgctttt gtgaatctcc actttgttca accccacccg ccgttctctc 540
ctccttgcgc cttcctctna ccttaanaac cagcttcctc tacccnatng tantttnctt 600
gcncnngtng aaattaattc ggtccnccgg aacctcttnc ctgtggcaac tgctnaaaga 660
aactgctgtt ctgnttactg cngtccc 687

<210> 39
<211> 695
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(695)
<223> n = A,T,C or G

<400> 39
actagtctgg cctacaatag tgtgattcat gtaggacttc tttcatcaat tcaaaacccc 60
tagaaaaacg tatacagatt atataagtag ggataagatt tctaacattt ctgggctctc 120
tgacccctgc gctagactgt ggaaagggag tattattata gtatacaaca ctgctgttgc 180
cttattagtt ataacatgat aggtgctgaa ttgtgattca caatttaaaa acactgtaat 240
ccaaactttt ttttttaact gtagatcatg catgtgaatg ttaatgttaa tttgttcaan 300
gttgttatgg gtagaaaaaa ccacatgcct taaaatttta aaaagcaggg cccaaactta 360
ttagtttaaa attaggggta tgtttccagt ttgttattaa ntggttatag ctctgtttag 420
aanaaatcna ngaacangat ttngaaantt aagntgacat tatttnccag tgacttgtta 480
atttgaaatc anacacggca ccttccgttt tggtnctatt ggnntttgaa tccaancngg 540
ntccaaatct tnttggaaac ngtccnttta actttttttac nanatcttat ttttttattt 600
tggaatggcc ctatttaang ttaaaagggg ggggnnccac naccattcnt gaataaaact 660
naatatatat ccttggtccc ccaaaattta aggng 695

<210> 40
<211> 674
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(674)
<223> n = A,T,C or G

<400> 40
actagtagtc agttgggagt ggttgctata ccttgacttc atttatatga atttccactt 60
tattaaataa tagaaaagaa aatcccggtg cttgcagtag agttatagga cattctatgc 120
ttacagaaaa tatagccatg attgaaatca aatagtaaag gctgttctgg ctttttatct 180
tcttagctca tcttaaataa gtagtacact tgggatgcag tgcgtctgaa gtgctaatca 240
gttgtaacaa tagcacaaat cgaacttagg atgtgtttct tctcttctgt gtttcgattt 300
tgatcaattc tttaattttg ggaacctata atacagtttt cctattcttg gagataaaaa 360
ttaaatggat cactgatatt taagtcattc tgcttctcat ctnaatattc catattctgt 420
attagganaa antacctccc agcacagccc cctctcaaac cccacccaaa accaagcatt 480
tggaatgagt ctcctttatt tccgaantgt ggatggtata acccatatcn ctccaatttc 540
tgnttgggtt gggtattaat ttgaactgtg catgaaaagn ggnaatcttt nctttgggtc 600
aaantttncc ggttaatttg nctngncaaa tccaatttnc tttaagggtg tctttataaa 660
atttgctatt cngg 674

<210> 41
<211> 657
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(657)
<223> n = A,T,C or G

<400> 41
gaaacatgca agtaccacac actgtttgaa ttttgcacaa aaagtgactg tagggatcag 60
gtgatagccc cggaatgtac agtgtcttgg tgcaccaaga tgccttctaa aggctgacat 120
accttgggac cctaatgggg cagagagtat agccctagcc cagtggtgac atgaccactc 180
cctttgggag gctgaagtta aagggaatgg tatgtgtttt ctcatggaag cagcacatga 240
atnggtnaca ngatgttaaa ntaaggntct antttgggtg tcttgtcatt tgaaaaantg 300
acacactcct ancanctggt aaaggggtgc tggaagccat ggaagaactc taaaaacatt 360
agcatgggct gatctgatta cttcctggca tcccgctcac ttttatggga agtcttatta 420
naaggatggg anantttttcc atatccttgc tgttggaact ctggaacact ctctaaattt 480
ccctctatta aaaatcactg nccttactac acttcctcct tganggaata gaaatggacc 540
tttctctgac ttagttcttg gcatggganc cagcccaaat taaaatctga cttntccggt 600
ttctccngaa ctcacctact tgaattggta aaacctcctt tggaattagn aaaaacc 657

<210> 42
<211> 389
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(389)
<223> n = A,T,C or G

<400> 42

actagtgctg aggaatgtaa acaagtttgc tgggccttgc gagacttcac caggttgttt 60
cgatagctca cactcctgca ctgtgcctgt cacccaggaa tgtcttttt aattagaaga 120
caggaagaaa acaaaaacca gactgtgtcc cacaatcaga aacctccgtt gtggcagang 180
ggccttcacc gccaccaggg tgtcccgcca gacagggaga gactccagcc ttctgaggcc 240
atcctgaaga attcctgttt gggggttgtg aaggaaaatc acccggattt aaaaagatgc 300
tgttgcctgc ccgcgtngtn gggaagggac tggtttcctg gtgaatttct taaaagaaaa 360
atattttaag ttaagaaaaa aaaaaaaaa 389

<210> 43
<211> 279
<212> DNA
<213> Homo sapien

<400> 43
actagtgaca agctcctggt cttgagatgt cttctcgtta aggagatggg ccttttggag 60
gtaaaggata aaatgaatga gttctgtcat gattcactat tctagaactt gcatgacctt 120
tactgtgtta gctctttgaa tgttcttgaa attttagact ttctttgtaa acaaataata 180
tgtccttatc attgtataaa agctgttatg tgcaacagtg tggagatcct tgtctgattt 240
aataaaatac ttaaacactg aaaaaaaaaa aaaaaaaaa 279

<210> 44
<211> 449
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(449)
<223> n = A,T,C or G

<400> 44
actagtagca tcttttctac aacgttaaaa ttgcagaagt agcttatcat taaaaaacaa 60
caacaacaac aataacaata aatcctaagt gtaaatcagt tattctaccc cctaccaagg 120
atatcagcct gtttttttcc ttttttctcc tgggaataat tgtgggcttc ttcccaaatt 180
tctacagcct ctttcctctt ctcatgcttg agcttccctg tttgcacgca tgcgttgtgc 240
aagantgggc tgtttngctt ggantncggt ccnagtggaa ncatgctttc ccttgttact 300
gttggaagaa actcaaacct tcnancccta ggtgttncca ttttgtcaag tcatcactgt 360
atttttgtac tggcattaac aaaaaaagaa atnaaatatt gttccattaa actttaataa 420
aactttaaaa gggaaaaaaa aaaaaaaaa 449

<210> 45
<211> 559
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(559)
<223> n = A,T,C or G

<400> 45
actagtgtgg gggaatcacg gacacttaaa gtcaatctgc gaaataattc ttttattaca 60
cacttactga agtttttgag tcccagagag ccattctatg tcaaacattc caagtacttt 120
ttgagagccc agcattacat caacatgccc gtgcagttca aaccgaagtc cgcaggcaaa 180
tttgaagctt tgcttgtcat tcaaacagat gaaggcaaga gtattgctat tcgactaatt 240

ggtgaagctc ttggaaaaaa ttnactagaa tacttttttgt gttaagttaa ttacataagt 300
tgtattttgt taactttatc tttctacact acaattatgc ttttgtatat atattttgta 360
tgatggatat ctataattgt agattttgtt tttacaagct aatactgaag actcgactga 420
aatattatgt atctagccca tagtattgta ctttaacttttt acagggtgaa aaaaaaattc 480
tgtgtttgca ttgattatga tattctgaat aaatatggga atatatttta atgtgggtaa 540
aaaaaaaaaa aaaaaggaa 559

<210> 46
<211> 731
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

<400> 46
actagtttta gtaccatggc tgtcatagat gcaaccatta tattccattt agttttttcc 60
tcaggttccc taacaattgt ttgaaactga atatatatgt ttatgtatgt gtgtgtgttc 120
actgttcatgt atatggtgta tatgggatgt gtgcagtttt cagttatata tatattcata 180
tatacatatg catatatatg tataatatac atatatacat gcatacactt gtataatata 240
catatatata cacatatatg cacacatatn atcactgagt ttcaaagtga gtcttttatt 300
ggggcaattg tatttttctcc ctctgttctgc tcactgggcc tttgcaagac atagcaattg 360
cttgatttcc tttggataag agtcttatct tcggcactct tgactctagc cttaacttta 420
gattttctatt ccagaatacc tctcatatct atcttaaaac ctaaganggg taaagangtc 480
ataagattgt agtatgaaag antttgctta gttaaattat atcttcaggaa actcattcat 540
ctacaaatta aattgtaaaa tgatggtttg ttgtatctga aaaaatgttt agaacaagaa 600
atgtaactgg gtacctgtta tatcaaagaa cctcnattta ttaagtctcc tcatagccan 660
atccttatat ngccctctct gacctgantt aatananact tgaataatga atagttaatt 720
taggnttggg c 731

<210> 47
<211> 640
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(640)
<223> n = A,T,C or G

<400> 47
tgcgngccgg tttggccctt ctttgtanga cactttcatc cgccctgaaa tcttcccgat 60
cgttaataac tcctcaggtc cctgcctgca cagggttttt tcttantttg ttgcctaaca 120
gtacaccaaa tgtgacatcc tttcaccaat atngattnct tcataccaca tcntcnatgg 180
anacgactnc aacaattttt tgatnacccn aaanactggg ggctnnaana agtacantct 240
ggagcagcat ggacctgtcn gcnactaang gaacaanagt nntgaacatt tacacaacct 300
ttggtatgtc ttactgaaag anagaaacat gcttctnncc ctagaccacg aggncaaccg 360
caganattgc caatgccaag tccgagcggt tagatcaggt aatacattcc atggatgcat 420
tacatacntt gtcccgaaa nanaagatgc cctaanggct tctttcanact ggtccngaaa 480
acanctacac ctggtgcttg ganaacanac tctttggaag atcatctggc acaagttccc 540
cccagtgggt tttnccttgg cacctanctt accanatcna ttcggaancc attctttgcc 600
ntggcnttnt nttgggacca ntctttctcac aactgnaccc 640

<210> 48
<211> 257
<212> DNA
<213> Homo sapien

<400> 48
acttagtatat gaaaatgtaa atatcacttg tgtactcaaa caaaagttgg tcttaagctt 60
ccaccttgag cagccttgga aacctaacct gcctctttta gcataatcac attttctaaa 120
tgattttctt tgttcctgaa aaagtgattt gtattagttt tacatttgtt ttttggaaga 180
ttatatttgt atatgtatca tcataaaata tttaaataaa aagtatcttt agagtgaaaa 240
aaaaaaaaaa aaaaaaa 257

<210> 49
<211> 652
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(652)
<223> n = A,T,C or G

<400> 49
actagttcag atgagtggct gctgaagggg cccccttgtc attttcatta taacccaatt 60
tccacttatt tgaactctta agtcataaat gtataatgac ttatgaatta gcacagttaa 120
gttgacacta gaaactgccc atttctgtat tacactatca aataggaaac attggaaaga 180
tggggaaaaa aatcttattt taaaatggct tagaaagttt tcagattact ttgaaaattc 240
taaacttctt tctgtttcca aaacttgaaa atatgtagat ggactcatgc attaagactg 300
ttttcaaagc tttcctcaca tttttaaagt gtgattttcc ttttaatata catatttatt 360
ttctttaaag cagctatatc ccaacccatg actttggaga tatacctatn aaaccaatat 420
aacagcangg ttattgaagc agctttctca aatgttgctt cagatgtgca agttgcaaat 480
tttattgtat ttgtanaata caatttttgt tttaaactgt atttcaatct atttctccaa 540
gatgcttttc atatagagtg aaatatccca ngataactgc ttctgtgtcg tcgcatttga 600
cgcataactg cacaaatgaa cagtgtatac ctcttggttg tgcattnacc cc 652

<210> 50
<211> 650
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(650)
<223> n = A,T,C or G

<400> 50
ttgcgctttg atttttttag ggcttgtgcc ctgtttcact tatagggtct agaatgcttg 60
tgttgagtaa aaaggagatg cccaatattc aaagctgcta aatgttctct ttgccataaa 120
gactccgtgt aactgtgtga acacttggga ttttttctcct ctgtcccgag gtcgtcgtct 180
gcttttcttt ttgggttctt tctagaagat tgagaaatgc atatgacagg ctgagancac 240
ctccccaaac acacaagctc tcagccacan gcagcttctc cacagcccca gcttcgcaca 300
ggctcctgga nggctgcctg ggggaggcag acatgggagt gccaaggtgg ccagatggtt 360
ccaggactac aatgtcttta tttttaactg tttgccactg ctgcccttcac ccctgcccgg 420
ctctggagta ccgtctgccc canacaagtg ggantgaaat gggggtgggg gggaacactg 480
attcccantt agggggtgcc taactgaaca gtagggatan aaggtgtgaa cctgngaant 540

gcttttataa attatnttcc ttgttanatt tatttttaa tttaatctct gttnaactgc 600
ccngggaaaa ggggaaaaaa aaaaaaaaat tctntttaaa cacatgaaca 650

<210> 51
<211> 545
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(545)
<223> n = A,T,C or G

<400> 51
tggcgtgcaa ccagggtagc tgaagtttgg gtctgggact ggagattggc cattaggcct 60
cctganattc cagctccctt ccaccaagcc cagtcttgct acgtggcaca gggcaaacct 120
gactcccttt gggcctcagt ttcccctccc cttcatgana tgaaaagaat actacttttt 180
cttgttggtc taacnttgct ggacncaaag tgtngtcatt attgttgtat tgggtgatgt 240
gtncaaaact gcagaagctc actgcctatg agaggaanta agagagatag tggatganag 300
ggacanaagg agtcattatt tggtatagat ccacccntcc caacctttct ctcctcagtc 360
cctgcncctc atgtntctgg tntggtgagt cctttgtgcc accanccatc atgctttgca 420
ttgctgccat cctgggaagg gggtgnatcg tctcacaact tgttgtcatc gtttganatg 480
catgcttttt tnatnaaaca aanaaannaa tgtttgacag ngtttaaaat aaaaaanaaa 540
caaaa 545

<210> 52
<211> 678
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(678)
<223> n = A,T,C or G

<400> 52
actagtagaa gaactttgcc gcttttgtgc ctctcacagg cgcctaaagt cattgccatg 60
ggaggaagac gatttggggg gggaggggggg gggggcangg tccgtggggc tttccctant 120
ntatctccat ntccantgnn cnntgtcgcc tcttcccccg tcncattnga anttantccc 180
tggncccccnn ncccctctcn ncctncncct ccccccctccg ncncctccnn ctttttntan 240
ncttccccat ctccntcccc cctnanngtc ccaacnccgn cagcaatnnc ncacttnctc 300
nctccncncc tccnnccgtt cttctnttct cnacntntnc ncnnntnccn tgccnntnaa 360
annctctccc cnctgcaanc gattctctcc ctccncnnan ctntccactc cntnctttct 420
ncncgctcct nttcntcnnc ccacctctcn ccttcgnccc cantacnctc nccncccttn 480
cgnntcnttn nnntcctcnn accncccncc tcccttcncc cctcttctcc ccggtntntc 540
tctctcccnc nncncnnccc cnnccccntcc nngcgnccnt ttccgccccn cnccnccntt 600
ccttcntcnc cantccatcn cntntnccat nctncctncc nctcacnccc gctncccccn 660
nttctctttca cacngtcc 678

<210> 53
<211> 502
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 53
tgaagatcct ggtgtcgcca tgggccgccg ccccgcccgt tgttaccggt attgtaagaa 60
caagccgtac ccaaagtctc gcttctgccg aggtgtccct gatgccaaaa ttcgcatttt 120
tgaccctgggg cggaaaaang caaaantgga tgagtctccg ctttgtggcc acatggtgtc 180
agatcaatat gagcagctgt cctctgaagc cctgnangct gcccgaattt gtgccaataa 240
gtacatggta aaaagtngtg gcnaagatgc ttccatatcc gggtgcggnt ccaccccttc 300
cacgtcatcc gcatcaacaa gatgttgtcc tgtgctgggg ctgacaggct cccaacaggc 360
atgcgaagtg cctttggaaa acccanggca ctgtggccag ggttcacatt gggccaattn 420
atcatgttca tccgcaccaa ctgcagaaca angaacntgt naattnaagc cctgcccagg 480
gncaanttca aatttcccgg cc 502

<210> 54
<211> 494
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 54
actagtccaa gaaaaatatg cttaatgtat attacaaagg ctttgtatat gttaaccctgt 60
tttaatgcca aaagtttgcc ttgtccacaa tttccttaag acctcttcag aaagggattt 120
gtttgcctta atgaatactg ttgggaaaaa acacagtata atgagtgaaa agggcagaag 180
caagaaattt ctacatctta gcgactccaa gaagaatgag tatccacatt tagatggcac 240
attatgagga ctttaatctt tccttaaaca caataatgtt ttctttttttc ttttattcac 300
atgatttcta agtatatttt tcatgcagga cagtttttca accttgatgt acagtgactg 360
tgttaaattt ttctttcagt ggcaaccttt ataatcttta aaatatggtg agcatcttgt 420
ctgttttgaa ngggatatga cnatnaatct atcagatggg aaatcctgtt tccaagttag 480
aaaaaaaaaa aaaa 494

<210> 55
<211> 606
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(606)
<223> n = A,T,C or G

<400> 55
actagtaaaa agcagcattg ccaaataatc cctaattttc cactaaaaat ataatgaaat 60
gatgttaagc tttttgaaaa gtttaggtta aacctactgt tgttagatta atgtatttgt 120
tgcttccctt tatctggaat gtggcattag ctttttttatt ttaaccctct ttaattctta 180
ttcaattcca tgacttaagg ttggagagct aaacactggg atttttggat aacagactga 240
cagttttgca taattataat cggcattgta catagaaagg atatggctac cttttgttaa 300
atctgcactt tctaaatatc aaaaaaggga aatgaagtat aaatcaattt ttgtataatc 360
tgtttgaaac atgantttta tttgcttaat attanggctt tgccctttttc tgttagtctc 420
ttgggatcct gtgtaaaact gttctcatta aacaccaaac agttaagtcc attcttctggt 480

actagctaca aattccgttt catattctac ntaacaattt aaattaactg aaatatttct 540
anatggtcta cttctgtcnt ataaaaacna aacttgantt nccaaaaaaa aaaaaaaaaa 600
aaaaaa 606

<210> 56
<211> 183
<212> DNA
<213> Homo sapien

<400> 56
actagtatat ttaaacttac aggcttattt gtaatgtaaa ccaccatttt aatgtactgt 60
aattaacatg gttataatac gtacaatcct tccctcatcc catcacacaa ctttttttgt 120
gtgtgataaa ctgattttgg tttgcaataa aaccttgaaa aataaaaaaa aaaaaaaaaa 180
aaa 183

<210> 57
<211> 622
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(622)
<223> n = A,T,C or G

<400> 57
actagtcact actgtcttct ccttgtagct aatcaatcaa tattcttccc ttgcctgtgg 60
gcagtggaga gtgctgctgg gtgtacgctg cacctgccca ctgagttggg gaaagaggat 120
aatcagtgag cactgttctg ctcagagctc ctgatctacc ccacccccta ggatccagga 180
ctgggtcaaa gctgcatgaa accaggccct ggcagcaacc tgggaatggc tggaggtggg 240
agagaacctg actttctttt ccctctccct cctccaacat tactggaact ctatcctgtt 300
agggatcttc tgagcttgtt tccctgctgg gtgggacaga agacaaagga gaagggangg 360
tctacaanaa gcagcccttc tttgtcctct ggggttaatg agcttgacct ananttcatg 420
gaganaccan aagcctctga ttttaattt ccntnaaatg tttgaagtnt atatntacat 480
atatatattt ctttnaatnt ttgagtcttt gatatgtctt aaaatccant ccctctgccn 540
gaaacctgaa ttaaaaccat gaanaaaaat gtttncctta aagatgttan taattaattg 600
aaacttgaaa aaaaaaaaaa aa 622

<210> 58
<211> 433
<212> DNA
<213> Homo sapien

<400> 58
gaacaaattc tgattggtta tgtaccgtca aaagacttga agaaatttca tgattttgca 60
gtgtggaagc gttgaaaatt gaaagttact gcttttccac ttgctcatat agtaaaggga 120
tcctttcagc tgccagtgtt gaataatgta tcatccagag tgatgttatc tgtgacagtc 180
accagcttta agctgaacca ttttatgaat accaaataaa tagaccttct gtactgaaaa 240
catatttgtg actttaatcg tgctgcttgg atagaaatat ttttactggt tcttctgaat 300
tgacagtaaa cctgtccatt atgaatggcc tactgttcta ttatttgttt tgacttgaat 360
ttatccacca aagacttcat ttgtgtatca tcaataaagt tgtatgtttc aactgaaaaa 420
aaaaaaaaaa aaa 433

<210> 59
<211> 649

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(649)
<223> n = A,T,C or G

<400> 59
actagttatt atctgacttt cnggttataa tcattctaat gagtgtgaag tagcctctgg 60
tgtcatttgg atttgcattt ctctgatgag tgatgctatc aagcaccttt gctggtgctg 120
ttggccatat gtgtatgttc cctggagaag tgtctgtgct gagccttggc ccactttttа 180
attaggcgtn tgtcttttta ttactgagtt gtaaganttc tttatatatt ctggattcta 240
gacccttatc agatacatgg tttgcaaata ttttctccca ttctgtgggt tgtgttttca 300
ctttatcgat aatgtcctta gacatataat aaatttgtat tttaaaagtg acttgatttg 360
ggctgtgcaa ggtgggctca cgcttgtaat cccagcactt tgggagactg aggtgggtgg 420
atcatatgan gangctagga gttcgaggtc agcctggcca gcatagcgaa aacttgtctc 480
tacnaaaaat acaaaaatta gtcaggcatg gtggtgcacg tctgtaatac cagctttcta 540
ggangctgan gcacaaggat cacttgaacc ccagaangaa gangttgcag tganctgaag 600
atcatgccag ggcaacaaaa atgagaactt gtttaaaaaa aaaaaaaaa 649

<210> 60
<211> 423
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(423)
<223> n = A,T,C or G

<400> 60
actagttcag gcattccagt tcactgacaa acatggggaa gtgtgcccag ctggctggaa 60
acctggcagt gataccatca agcctgatgt ccaaaagagc aaagaatatt tctccaagca 120
gaagtgagcg ctgggctgtt ttagtgccag gctgcggtgg gcagccatga gaacaaaacc 180
tcttctgtat tttttttttc cattagtana acacaagact cngattcagc cgaattgtgg 240
tgtcttacaa ggcagggctt tcctacaggg ggtgganaaa acagcctttc ttcctttggt 300
aggaatggcc tgagttggcg ttgtgggcag gctactggtt tgtatgatgt attagtagag 360
caacccatta atcttttgta gtttgtatna aacttganct gagaccttaa acaaaaaaaa 420
aaa 423

<210> 61
<211> 423
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(423)
<223> n = A,T,C or G

<400> 61
cgggactgga atgtaaagtg aagttcggag ctctgagcac gggctctttc cgccgggtcc 60
tccctcccca gatcccagag ggagaggccc accccgccca gccccgcccc agccccctgct 120
caggttctgag tatggctggg agtcgggggc cacaggcctc tagctgtgct gctcaagaag 180

actggatcag ggtanctaca agtggccggg ccttgccttt gggattctac cctgttccta 240
atttggtgtt ggggtgcggg gtccctggcc ccctttttcca cactncctcc ctccngacag 300
caacctcccc tggggcaatt gggcctggnt ctccncccgn tgttgcnacc ctttgttggt 360
ttaaggnctt taaaaatgtt annttttccc ntgccngggt taaaaaagga aaaaactnaa 420
aaa 423

<210> 62
<211> 683
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(683)
<223> n = A,T,C or G

<400> 62
gctggagagg ggtacggact ttcttggagt tgtcccaggt tggaatgaga ctgaactcaa 60
gaagagaccc taagagactg gggaatggtt cctgccttca ggaaagtgaa agacgcttag 120
gctgtcaaca cttaaaggaa gtccccttga agcccagagt ggacagacta gacccattga 180
tggggccact ggccatggtc cgtggacaag acattccngt gggccatggc acaccggggg 240
ggatcaaaat gtgtacttgt ggggtctcgc ccattgccaa aaccaaacca ntcccacttc 300
tgtcnttgga cttttcttcc attcccctcc cccaaatgc acttcccctc ctcccctctgc 360
ccctcctgtg tttttggaat tctgtttccc tcaaaattgt taatttttta nttttngacc 420
atgaacttat gtttgggggtc nangttcccc ttnccaatgc atactaatat attaatggtt 480
atttattttt gaaatatttt ttaatgaact tggaaaaaat tnntggaatt tcctttnttc 540
cnttttnttt ggggggggtg gggggntggg ttaaaatttt tttggaancc cnatnggaaa 600
ttnttacttg gggccccccc naaaaaantn anttccaatt cttnnatngc ccctnttccn 660
ctaaaaaaaa ananannaaa aan 683

<210> 63
<211> 731
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

<400> 63
actagtcata aagggtgtgc gcgtcttcga cgtggcggtc ttggcgccac tgctgcgaga 60
cccggccctg gacctcaagg tcatccactt ggtgcgtgat ccccgcgcgg tggcgagttc 120
acggatccgc tcgcgccacg gcctcatccg tgagagccta caggtggtgc gcagccgaga 180
ccgcgagctc accgcatgcc cttcttggag gccgcgggcc acaagcttgg cgcccanaaa 240
gaaggcgtng ggggcccgca aantaccacg ctctgggcgc tatggaangt cctcttgcaa 300
taatattggt tnaaaanctg canaanagcc cctgcanccc cctgaactgg gntgcagggc 360
cncttacctn gtttggntgc ggttacaaag aacctgtttn ggaaaaccct nccnaaaacc 420
ttccgggaaa attntncaaa ttttttnttgg ggaattnttg ggtaaacccc ccnaaaatgg 480
gaaacntttt tgccctnnaa antaaaccat tnggttccgg gggccccccc ncaaaaccct 540
ttttttnttt tttntgcccc cantnnnccc ccggggcccc ttttttttngg ggaaaanccc 600
ccccccctncc nanantttta aaagggnggg anaatttttn nttnccccnc gggnccccnn 660
ggngntaaaa nggtttcncc ccccccgaggg gnggggnnnc ctcnnaaacc cntntcnnna 720
ccncnttttn n 731

<210> 64
<211> 313
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(313)
<223> n = A,T,C or G

<400> 64
actagttgtg caaaccacga ctgaagaaag acgaaaagtg ggaaataact tgcaacgtct 60
gttagagatg gttgctacac atgttgggtc tgtagagaaa catcttgagg agcagattgc 120
taaagttgat agagaatatg aagaatgcat gtcagaagat ctctcggaaa atattaaaga 180
gattagagat aagtatgaga agaaagctac tctaattaag tcttctgaag aatgaagatn 240
aaatgttgat catgtatata tatccatagt gaataaaatt gtctcagtaa agttgtaaaa 300
aaaaaaaaaa aaa 313

<210> 65
<211> 420
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(420)
<223> n = A,T,C or G

<400> 65
actagttccc tggcaggcaa gggcttccaa ctgaggcagt gcatgtgtgg cagagagagg 60
caggaagctg gcagtggcag cttctgtgtc tagggagggg tgtggctccc tccttccctg 120
tctgggaggt tggagggaag aatctaggcc ttagcttgcc ctcctgccac cctttccctt 180
gtagatactg ccttaacact ccctcctctc tcagctgtgg ctgccaccca agccaggttt 240
ctccgtgctc actaatttat ttccaggaaa ggtgtgtgga agacatgagc cgtgtataat 300
atttgtttta acatttttcat tgcaagtatt gaccatcatc cttggttgtg tatcgttgta 360
acacaaatta atgatattaa aaagcatcca aacaaagccn annnnnaana nnannngaaa 420

<210> 66
<211> 676
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(676)
<223> n = A,T,C or G

<400> 66
actagtttcc tatgatcatt aaactcattc tcagggttaa gaaaggaatg taaatttctg 60
cctcaatttg tacttcatca ataagttttt gaagagtgca gatttttagt caggtcttaa 120
aaataaactc acaaatctgg atgcatttct aaattctgca aatgtttcct ggggtgactt 180
aacaaggaat aatcccacaa tatacctagc tacctaatac atggagctgg ggctcaaccc 240
actgttttta aggatttgcg cttacttgtg gctgaggaaa aataagtagt tccgagggaa 300
gtagttttta aatgtgagct tatagatngg aaacagaata tcaacttaat tatggaaatt 360
gttagaaacc tgttctcttg ttatctgaat cttgattgca attactattg tactggatag 420

actccagccc attgcaaagt ctcagatatc ttanctgtgt agttgaattc cttggaaatt 480
ctttttaaga aaaaattgga gtttnaaaga aataaacccc tttgttaaat gaagcttggc 540
tttttggtga aaaanaatca tcccgcaggg cttattgttt aaaaanggaa ttttaagcct 600
ccctggaaaa anttgttaat taaatgggga aaatgntggg naaaaattat ccgttagggt 660
ttaaagggaa aactta 676

<210> 67
<211> 620
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(620)
<223> n = A,T,C or G

<400> 67
caccattaaa gctgcttacc aagaacttcc ccagcatttt gacttccttg tttgatagct 60
gaattgtgag caggtgatag aagagccttt ctagttgaac atacagataa tttgctgaat 120
acattccatt taatgaaggg gttacatctg ttacgaagct actaagaagg agcaagagca 180
taggggaaaa aaatctgatc agaacgcatc aaactcacat gtgccccctc tactacaaac 240
agattgtagt gctgtggtgg tttattccgt tgtgcagaac ttgcaagctg agtcactaaa 300
cccaaagaga ggaaattata ggttagttaa acattgtaat cccaggaact aagtttaatt 360
cacttttgaa gtgttttgtt ttttatttct ggtttgtctg atttactttg ggggaaaang 420
ctaaaaaaaa agggatatca atctctaatt cagtgcccac taaaagttgt ccctaaaaag 480
tcttttactgg aanttatggg acttttttaag ctccaggtnt tttggtcctc caaattaacc 540
ttgcatgggc cccttaaaat tgttgaangg cattcctgcc tctaagtttg gggaaaattc 600
ccccnttttn aaaatttgga 620

<210> 68
<211> 551
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(551)
<223> n = A,T,C or G

<400> 68
actagtagct ggtacataat cactgaggag ctatttctta acatgctttt atagaccatg 60
ctaatgctag accagtattt aagggctaat ctcacacctc cttagctgta agagtctggc 120
ttagaacaga cctctctgtg caataacttg tggccactgg aaatccctgg gccggcattt 180
gtattggggt tgcaatgact cccaagggcc aaaagagtta aaggcacgac tgggatttct 240
tctgagactg tggtgaaact ccttccaagg ctgagggggt cagtangtgc tctgggaggg 300
actcggcacc actttgatat tcaacaagcc acttgaagcc caattataaa attgttattt 360
tacagctgat ggaactcaat ttgaaccttc aaaactttgt tagtttatcc tattatattg 420
ttaaacctaa ttacatttgt ctagcattgg atttggttcc tgtngcatat gttttttccn 480
cctatgtgct ccccttcccc nnatcttaat ttaaaccnca attttgcnat tcnccnnnnn 540
nannnannna a 551

<210> 69
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 69
cagaaatgga aagcagagtt ttcatttctg tttataaacg tctccaaaca aaaatggaaa 60
gcagagtttt cattaaatcc ttttaccttt ttttttttctt ggtaatcccc tcaaataaca 120
gtatgtggga tattgaatgt taaagggata ttttttttcta ttatttttat aattgtacaa 180
aattaagcaa atgttaaaag ttttatatgc tttattaatg ttttcaaaag gtatnataca 240
tgtgatacat tttttaagct tcagttgctt gtcttctggt actttctgtt atgggctttt 300
ggggagccan aaaccaatct acnatctctt tttgtttgcc aggacatgca ataaaattta 360
aaaaataaat aaaaactatt nagaaattga aaaaaa 396

<210> 70
<211> 536
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(536)
<223> n = A,T,C or G

<400> 70
actagtgcaa aagcaaatat aaacatcgaa aaggcgttcc tcacgttagc tgaagatatc 60
ctttgaaaga cccctgtaaa agagcccaac agtgaaaatg tagatatcag cagtggagga 120
ggcgtgacag gctggaagag caaatgctgc tgagcattct cctgttccat cagttgccat 180
ccactacccc gttttctctt cttgctgcaa aataaaccac tctgtccatt tttaacttta 240
aacagatatt tttgtttctc atcttaacta tccaagccac ctatttttatt tgttctttca 300
tctgtgactg cttgctgact ttatcataat tttcttcaaa caaaaaaatg tatagaaaaa 360
tcatgtctgt gactttcattt ttaaatgnta cttgctcagc tcaactgcat ttcagttgtt 420
ttatagtcca gttcttatca acattnaaac ctatngcaat catttcaaat ctatttctgca 480
aattgtataa gaataaaagt tagaatttaa caattaaaaa aaaaaaaaaa aaaaaa 536

<210> 71
<211> 865
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(865)
<223> n = A,T,C or G

<400> 71
gacaaagcgt taggagaaga anagaggcag ggaanactnc ccaggcacga tggccnccct 60
cccaccagca accagcgccc cccaccagcc cccaggcccg gacgacgaag actccatcct 120
ggattaatct nacctctntc gcctgnccca ttcctacctc ggaggtggag gccggaaagg 180
tcncaccaag aganaanctg ctgccaacac caaccgcccc agcccctggcg ggcacganag 240
gaaactggtg accaatctgc agaattcctna gaggaanaag cnaggggccc cgcgctnaga 300
cagagctgga tatgangcca gaccatggac nctacncccn ncaatncana cgggactgcg 360
gaagatggan gacccncgac nngatcaggc cngctnncca nccccccacc cctatgaatt 420
attcccgctg aangaatctc tgannggctt ccannaaagc gcctcccccnc cnaacgnaan 480

tncaacatng ggattanang ctgggaactg naaggggcaa ancctnnaat atccccagaa 540
acaanctctc ccnaanaaac tggggcncct catnggtggn accaactatt aactaaaccg 600
cacgccaagn aantataaaa gggggggccc tccncggnng accccctttt gtcccttaat 660
ganggttatc cnccttgcgt accatggtnc ccnnttctgt ntgnatgttt ccnctccccc 720
ccncctatnt cnagccgaac tcnnatttnc ccgggggtgc natcnantng tncnccttcn 780
ttngttgncc cngccctttc cgncggaacn cgtttccccg ttantaacgg cacccggggn 840
aagggtgntt ggcccccccc ctccc 865

<210> 72
<211> 560
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(560)
<223> n = A,T,C or G

<400> 72
cctggacttg tcttggttcc agaacctgac gacccggcga cggcgacgtc tcttttgact 60
aaaagacagt gtccagtgct ccngcctagg agtctacggg gaccgcctcc cgcgccgcca 120
ccatgcccaa ctttctctggc aactggaaaa tcatccgatc ggaaaacttc gangaattgc 180
tcnaantgct gggggtgaat gtgatgctna ngaanattgc tgtggcngca gcgtccaagc 240
cagcagtgga gatcnaacag gagggagaca ctttctacat caaaacctcc accaccgtgc 300
gcaccacaaa gattaacttc nnngttgggg aggantttga ggancaaact gtggatngga 360
ngcctgtnaa aaccctggtga aatgggagaa tganaataaa atggtctgtg ancanaaact 420
cctgaaagga gaaggccccc anaactcctg gaccngaaaa actgaccccnc cnatngggga 480
actgatnctt gaaccctgaa cgggcgggat gancctttct tnttgccncc naangggttc 540
tttccntttc cccaaaaaaa 560

<210> 73
<211> 379
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(379)
<223> n = A,T,C or G

<400> 73
ctggggancc ggcggtnngc nccatntcnn gncgcgaagg tggcaataaa aanccnctga 60
aaccgcncaa naaacatgcc naagatatgg acgaggaaga tngngctttc nngnacaanc 120
gnanngagga acanaacaaa ctcnangagc tctcaagcta atgccgcggg gaaggggccc 180
ttggccacnn gtggaattaa gaaatctggc aaannngtann tgttccttgt gcctnangag 240
ataagngacc ctttatttca tctgtattta aacctctctn ttcccctgnca taacttcttt 300
tnccacgtan agntggaant anttgttgtc ttggactgtt gtncatttta gannaaactt 360
ttgttcaaaa aaaaaataa 379

<210> 74
<211> 437
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(437)
<223> n = A,T,C or G

<400> 74
actagttcag actgccacgc caaccccaga aaatacccca catgccagaa aagtgaagtc 60
ctaggtgttt ccatctatgt ttcaatctgt ccatctacca ggcctcgcga taaaaacaaa 120
acaaaaaaac gctgccaggt tttanaagca gttctggtct caaaaccatc aggatcctgc 180
caccagggtt cttttgaaat agtaccacat gtaaaaggga atttggcttt cacttcatct 240
aatcactgaa ttgtcaggct ttgattgata attgtagaaa taagtagcct tctgttgtgg 300
gaataagtta taatcagtat tcatctcttt gttttttgtc actcttttct ctctnattgt 360
gtcatttgta ctgtttgaaa aatatttctt ctataaaatt aaactaacct gccttaaaaa 420
aaaaaaaaaa aaaaaaa 437

<210> 75
<211> 579
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(579)
<223> n = A,T,C or G

<400> 75
ctccgtcgcc gccaagatga tgtgcggggc gccctccgcc acgcagccgg ccaccgccga 60
gacccagcac atcgccgacc aggtgaggtc ccagcttgaa gagaaagaaa acaagaagtt 120
ccctgtgttt aaggccgtgt cattcaagag ccaggtggtc gcggggacaa actacttcat 180
caaggtgcac gtcggcgacg aggacttcgt acacctgcga gtgttccaat ctctccctca 240
tgaaaacaag ccctgacct tatctaacta ccagaccaac aaagccaagc atgatgagct 300
gacctatttc tgatcctgac tttggacaag gcccttcagc cagaagactg acaaagtcat 360
cctccgtcta ccagagcgtg cacttgtgat cctaaaataa gcttcatctc cgggctgtgc 420
ccttggggtg gaaggggcan gatctgcact gcttttgcat ttctcttccc aaatttcatt 480
gtgttgattc tttccttcca ataggtgatc ttnattactt tcagaatatt ttccaaatna 540
gatatatttt naaaatcctt aaaaaaaaaa aaaaaaaaa 579

<210> 76
<211> 666
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(666)
<223> n = A,T,C or G

<400> 76
gtttatccta tcttttccaac cagattgtca gctccttgag ggcaagagcc acagtatatt 60
tcccctgttc ttccacagtg cctaataata ctgtggaact aggttttaat aatttttaa 120
ttgatgttgt tatgggcagg atggcaacca gaccattgtc tcagagcagg tgctggctct 180
ttcctggcta ctccatgttg gctagcctct ggtaacctct tacttattat cttcaggaca 240
ctcactacag ggaccaggga tgatgcaaca tccttgtctt tttatgacag gatgtttgct 300
cagcttctcc aacaataaaa agcacgtggt aaaacacttg cggatattct ggactgtttt 360
taaaaaatat acagtttacc gaaaatcata ttatcttaca atgaaaagga nttttatagat 420
cagccagtga acaacctttt cccaccatac aaaaattcct tttcccgaan gaaaanggct 480

ttctcaataa ncctcacttt cttaanatct tacaagatag ccccganatc ttatcgaaac 540
tcattttagg caaatatgan ttttattgtn cgttacttgt ttcaaaattt ggtattgtga 600
atatcaatta ccacccccat ctcccatgaa anaaanggga aanggtgaan ttcntaancg 660
cttaaa 666

<210> 77
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 77
ctgcagcccg ggggatccac taatctacca nggttatttg gcagctaatt ctanatttgg 60
atcattgccc aaagttgcac ttgctggtct cttgggattt ggccttggaa aggtatcata 120
catanganta tgccanaata aattccattt ttttgaaaat canctccntg gggctggttt 180
tggtccacag cataacangc actgcctcct tacctgtgag gaatgcaaaa taaagcatgg 240
attaagtgag aagggagact ctcagccttc agcttcctaa attctgtgtc tgtgactttc 300
gaagtttttt aaacctctga atttgtacac atttaaaatt tcaagtgtac tttaaaataa 360
aatacttcta atgggaacaa aaaaaaaaaa aaaaaa 396

<210> 78
<211> 793
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(793)
<223> n = A,T,C or G

<400> 78
gcatcctagc cgccgactca cacaaggcag gtgggtgagg aaatccagag ttgccatgga 60
gaaaattcca gtgtcagcat tcttgctcct tgtggccctc tcctacactc tggccagaga 120
taccacagtc aaacctggag ccaaaaagga cacaaaggac tctcgaccca aactgcccca 180
gacccctctcc agaggttggg gtgaccaact catctggact cagacatatg aagaagcctt 240
atataaatcc aagacaagca acaaaccctt gatgattatt catcacttgg atgagtgccc 300
acacagtcna gctttaaaga aagtgtttgc tgaaaataaa gaaatccaga aattggcaga 360
gcagtttgtc ctcctcaatc tggtttatga aacaactgac aaacaccttt ctcctgatgg 420
ccagtatgtc ccaggattat gtttgttgac ccatctctga cagttgaagc cgatatcctg 480
ggaagatatt cnaaccgtct ctatgcttac aaactgcaga tacgctctgt tgcttgacac 540
atgaaaaagc tctcaagttg ctnaaaatga attgtaagaa aaaaaatctc cagccttctg 600
tctgtcggct tgaaaattga aaccagaaaa atgtgaaaaa tggctattgt ggaacanatn 660
gacacctgat taggttttgg ttatgttcac cactattttt aanaaaanan nttttaaaat 720
ttggttcaat tntctttttn aaacaatntg tttctacntt gnganctgat ttctaaaaaa 780
aataatnttt ggc 793

<210> 79
<211> 456
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(456)
<223> n = A,T,C or G

<400> 79
actagtatgg ggtgggaggc cccacccttc tcccctaggc gctgttcttg ctccaaaggg 60
ctccgtggag agggactggc agagctgang ccacctgggg ctggggatcc cactcttctt 120
gcagctgttg agcgcaccta accactggtc atgccccccac ccctgctctc cgcacccgct 180
tcctcccgac cccangacca ggctacttct cccctcctct tgcctccctc ctgccccctgc 240
tgcctctgat cgtangaatt gangantgtc ccgccttgtg gctganaatg gacagtggca 300
ggggctggaa atgggtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gcnccccccc 360
tgcaagaccg agattgaggg aaancatgtc tgctgggtgt gaccatgttt cctctccata 420
aantnccccc gtgacnctca naaaaaaaaa aaaaaa 456

<210> 80
<211> 284
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(284)
<223> n = A,T,C or G

<400> 80
ctttgtacct ctagaaaaga taggtattgt gtcatgaaac ttgagtttaa attttatata 60
taaaactaaa agtaatgctc actttagcaa cacatactaa aattggaacc atactgagaa 120
gaatagcatg acctccgtgc aaacaggaca agcaaatttg tgatgtgttg attaaaaaga 180
aataaataaa tgtgtatatg tgtaacttgt atgtttatgt ggaatacaga ttgggaaata 240
aaatgtattt cttactgtga aaaaaaaaaa aaaaaaaaaa aana 284

<210> 81
<211> 671
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(671)
<223> n = A,T,C or G

<400> 81
gccaccaaca ttccaagcta ccctgggtac ctttgtgcag tagaagctag tgagcatgtg 60
agcaagcggt gtgcacacgg agactcatcg ttataattta ctatctgcca agagtagaaa 120
gaaaggctgg ggatatttgg gttggcttgg ttttgatttt ttgcttgttt gtttgttttg 180
tactaaaaca gtattatctt ttgaatatcg tagggacata agtatataca tgttatccaa 240
tcaagatggc tagaatggtg cctttctgag tgtctaaaac ttgacacccc tggtaaatct 300
ttcaacacac ttccactgcc tgcgtaatga agttttgatt catttttaac cactggaatt 360
tttcaatgcc gtcatttttca gttagatnat tttgcacttt gagattaaaa tgccatgtct 420
atttgattag tcttatttttt ttatttttac aggcttatca gtctcactgt tggctgtcat 480
tgtgacaaag tcaaataaac ccccnaggac aacacacagt atgggatcac atattgtttg 540
acattaagct ttggccaaaa aatgttgcat gtgttttacc tcgacttgct aaatcaatan 600
canaaaggct ggcnnataat gttggtggtg aaataattaa tnantaacca aaaaaaaaan 660
aaaaaaaaaa a 671

<210> 82
<211> 217
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(217)
<223> n = A,T,C or G

<400> 82
ctgcagatgt ttcttgaatg ctttgtcaaa ttaanaaagt taaagtgcaa taatgtttga 60
agacaataag tggtggtgta tcttgtttct aataagataa actttttttgt ctttgcttta 120
tcttattagg gagttgtatg tcagtgtata aaacatactg tgtggtataa caggcttaat 180
aaattctttа aaaggaaaaa aaaaaaaaaa aaaaaaa 217

<210> 83
<211> 460
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(460)
<223> n = A,T,C or G

<400> 83
cgcgagtggg agcaccagga tctcgggctc ggaacgagac tgcacggatt gttttaagaa 60
aatggcagac aaaccagaca tgggggaaat cgccagcttc gatnaggcca agctgaanaa 120
aacggagacg caggagaaga acaccctgcc gaccaaagag accattgagc angagaagcg 180
gagtgaaatt tcctaagatc ctggaggatt tcctaccccc gtcctcttcg agaccccagt 240
cgtgatgtgg aggaagagcc acctgcaaga tggacacgag ccacaagctg cactgtgaac 300
ctgggcactc cgcgccgatg ccaccggcct gtgggtctct gaagggaccc cccccaatcg 360
gactgccaaa ttctccggtt tgccccggga tattatacaa nattatttgt atgaataatg 420
annataaaac acacctcgtg gcancaaana aaaaaaaaaa 460

<210> 84
<211> 323
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(323)
<223> n = A,T,C or G

<400> 84
tggtggatct tggctctgtg gagctgctgg gacgggatct aaaagactat tctggaagct 60
gtggtccaan gcattttgct ggcttaacgg gtcccggaac aaaggacacc agcctctaa 120
aattgaagtt tacccganat aacaatcttt tgggcagaga tgcctatttt aacaaacncc 180
gtcccctgcgc aacaacnaac aatctctggg aaataccggc catgaacntg ctgtctcaat 240
cnancatctc tctagctgac cgatcatatc gtcccagatt actacanatc ataataattg 300
atttcctgta naaaaaaaaa aaa 323

<210> 85
<211> 771
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(771)
<223> n = A,T,C or G

<400> 85
aaactgggta ctcaacactg agcagatctg ttctttgagc taaaaaccat gtgctgtacc 60
aanagtttgc tcctggctgc tttgatgtca gtgctgctac tccaccctgg cggcgaatca 120
gaagcaagca actttgactg ctgtcttgga tacacagacc gtattcttca tcctaaattt 180
attgtgggct tcacacggca gctggccaat gaaggctgtg acatcaatgc tatcatcttt 240
cacacaaaga aaaagttgtc tgtgtgcgca aatccaaaac agacttgggt gaaatatatt 300
gtgcgtctcc tcagtaaaaa agtcaagaac atgtaaaaac tgtggctttt ctggaatgga 360
attggacata gcccaagaac agaaagaact tgctggggtt ggaggtttca cttgcacatc 420
atgganggtt tagtgcttat cttatttgtg cctcctggac ttgtccaatt natgaagtta 480
atcatattgc atcatanttt gctttgttta acatcacatt naaattaaac tgtattttat 540
gttatttata gctntaggtt ttctgtgttt aacttttttat acnaantttc ctaaactatt 600
ttggtntant gcaanttaaa aattatattt ggggggggaa taaatattgg antttctgca 660
gccacaagct ttttttaaaa aaccantaca nccnngttaa atggtnggtc ccnaatggtt 720
tttgcttttn antagaaaat ttnttagaac natttgaaaa aaaaaaaaaa a 771

<210> 86
<211> 628
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(628)
<223> n = A,T,C or G

<400> 86
actagtttgc tttacatttt tgaaaagtat tatttttgtc caagtgctta tcaactaaac 60
cttgtgttag gtaagaatgg aatttattaa gtgaatcagt gtgacccttc ttgtcataag 120
attatcttaa agctgaagcc aaaatatgct tcaaaagaaa angactttat tgttcattgt 180
agttcataca ttcaaagcat ctgaactgta gtttctatag caagccaatt acatccataa 240
gtggagaang aaatagatta atgtcnaagt atgattggtg gagggagcaa ggttgaagat 300
aatctggggt tgaaattttc tagttttcat tctgtacatt tttagttnga catcagattt 360
gaaatattaa tgtttacctt tcaatgtgtg gtatcagctg gactcantaa cacccctttc 420
ttcccctnggg gatggggaat ggattattgg aaaatggaaa gaaaaaagta cttaaagcct 480
tcctttcnca gtttctggct cctaccctac tgatttancc agaataagaa aacattttat 540
catcntctgc tttattccca ttaatnaant tttgatgaat aaatctgctt ttatgcnnac 600
ccaaggaatt nagtggnttc ntcnttgt 628

<210> 87
<211> 518
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(518)
<223> n = A,T,C or G

<400> 87
ttttttattt tttttagaga gtagttcagc ttttatttat aaatttattg cctgttttat 60
tataacaaca ttatactgtt tatggtttaa tacatatggt tcaaaatgta taatacatca 120
agtagtacag ttttaaaatt ttatgcttaa aacaagtttt gtgtaaaaaa tgcagataca 180
ttttacatgg caaatcaatt tttaagtcat cctaaaaatt gatttttttt tgaaatttaa 240
aaacacattt aatttcaatt tctctcttat ataaccttta ttactatagc atggtttcca 300
ctacagttta acaatgcagc aaaattccca tttcacggta aattgggttt taagcggcaa 360
ggttaaaatg ctttgaggat cctnaatacc ctttgaactt caaatgaagg ttatggttgt 420
naatttaacc ctcatgccat aagcagaagc acaagtttag ctgcattttg ctctaaactg 480
taaaancgag cccccgttg aaaaagcaaa agggaccc 518

<210> 88
<211> 1844
<212> DNA
<213> Homo sapien

<400> 88
gagacagtga atcttagtat caaaggattt ttggcctcag aaaaagttgt tgattatttt 60
tattttattt tattttttcga gactccgtct caaaaaaaaa aaaaaaaaaa agaatcacaa 120
ggtatttgct aaagcatttt gagctgcttg gaaaaagggа agtagttgca gtagagtttc 180
ttccatcttc ttggtgctgg gaagccatat atgtgtcttt tactcaagct aaggggtata 240
agcttatgtg ttgaatttgc tacatctata tttcacatat tctcacaata agagaatttt 300
gaaatagaaa tatcatagaa catttaagaa agtttagtat aaataatatt ttgtgtgttt 360
taatcccttt gaagggatct atccaaagaa aatattttac actgagcttc ttcctacacg 420
tctcagtaac agatcctgtg ttagtctttg aaaatagctc atttttttaaa tgtcagtgag 480
tagatgtagc atacatatga tgtataatga cgtgtattat gttaacaatg tctgcagatt 540
ttgtaggaat acaaaacatg gccttttta taagcaaaac gggccaatga ctagaataac 600
acatagggca atctgtgaat atgtattata agcagcattc cagaaaagta gttggtgaaa 660
taattttcaa gtcaaaaagg gatatggaaa gggaattatg agtaaccttt atttttaag 720
ccttgctttt aaattaaacg ctacagccat ttaagccttg aggataataa agcttgagag 780
taataatgtt aggttagcaa aggtttagat gtatcacttc atgcatgcta ccatgatagt 840
aatgcagctc ttcgagtcat ttctggtcat tcaagatatt caccctttg cccatagaaa 900
gcaccctacc tcacctgctt actgacattg tcttagctga tcacaagatc attatcagcc 960
tccattattc cttactgtat ataaaataca gagttttata ttttcctttc ttcgttttc 1020
accatattca aaacctaaat ttgtttttgc agatggaatg caaagtaatc aagtgttcgt 1080
gctttcacct agaagggtgt ggtcctgaag gaaagaggtc cctaaatatc ccccaccctg 1140
ggtgctcctc cttccctggt accctgacta ccagaagtca ggtgctagag cagctggaga 1200
agtgcagcag cctgtgcttc cacagatggg ggtgctgctg caacaaggct ttcaatgtgc 1260
ccatcttagg gggagaagct agatcctgtg cagcagcctg gtaagtcctg aggaggttcc 1320
attgctcttc ctgctgctgt cctttgcttc tcaacggggc tcgctctaca gtctagagca 1380
catgcagcta acttgtgcct ctgcttatgc atgagggtta aattaacaac cataacctte 1440
atttgaagtt caaaggtgta ttcaggatcc tcaaagcatt ttaaccttgc cgcttaaaac 1500
ccaatttacc gtgaaatggg aattttgctg cattgttaaa ctgtagtgga aaccatgcta 1560
tagtaataaa ggttatataa gagagaaatt gaaattaaat gtgtttttaa atttcaaaaa 1620
aaaatcaatc tttaggatga cttaaaaatt gatttgccat gtaaaatgta tctgcatttt 1680
ttacacaaaa cttgttttaa gcataaaatt ttaaaactgt actacttgat gtattataca 1740
ttttgaacca tatgtattaa accataaaca gtataatgtt gttataataa aacaggcaat 1800
aaatttataa ataaaagctg aaaaaaaaaa aaaaaaaaaa aaaa 1844

<210> 89
<211> 523
<212> DNA

<213> Homo sapi n

<220>
<221> misc_feature
<222> (1)...(523)
<223> n = A,T,C or G

<400> 89
tttttttttt ttttttagt caatccacat ttattgatca cttattatgt accaggcact 60
gggataaaga tgactgttag tcactcacag taaggaagaa aactagcaaa taagacgatt 120
acaatatgat gtagaaaatg ctaagccaga gatatagaaa ggtcctattg ggtccttctg 180
tcaccttgtc tttccacatc cctacccttc acaggccttc cctccagctt cctgcccccg 240
ctccccactg cagatccccc gggatttttgc ctagagctaa acgagganat gggccccctg 300
gccctggcat gacttgaacc caaccacaga ctgggaaagg gagcctttcg anagtggatc 360
actttgatna gaaaacacat agggaattga agagaaantc cccaaatggc cacccgtgct 420
ggtgctcaag aaaagtttgc agaatggata aatgaaggat caagggaatt aatanatgaa 480
taattgaatg gtggctcaat aagaatgact ncnttgaatg acc 523

<210> 90
<211> 604
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(604)
<223> n = A,T,C or G

<400> 90
ccagtgtggt ggaatgcaaa gattaccccg gaagctttcg agaagctggg attccctgca 60
gcaaaggaaa tagccaatat gtgtcgtttc tatgaaatga agccagaccg agatgtcaat 120
ctcacccacc aactaaatcc caaagtcaaa agcttcagcc agtttatctc agagaaccag 180
gggagccttc aagggcatgt agaaaatcag ctgttcagat aggcctctgc accacacagc 240
ctctttcctc tctgatcctt ttcctctttа cggcacaaca ttcatgtttg acagaacatg 300
ctggaatgca attgtttgca acaccgaagg atttcctgcg gtcgcctctt cagtaggaag 360
cactgcattg gtgataggac acggtaattt gattcacatt taacttgcta gttagtgata 420
aggggtggta cacctgtttg gtaaaatgag aagcctcgga aacttgggag cttctctcct 480
accactaatg gggagggcag attattactg ggatttctcc tggggtgaat taatttcaag 540
ccctaattgc tgaaattccc ctnggcaggc tccagttttc tcaactgcat tgcaaaattc 600
cccc 604

<210> 91
<211> 858
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(858)
<223> n = A,T,C or G

<400> 91
ttttttttct ttttttttta tgattattat ttttttatt gatctttaca tcctcagtgt 60
tggcagagtt tctgatgctt aataaacatt tgttctgatc agataagtgg aaaaaattgt 120
catttcctta ttcaagccat gcttttctgt gatattctga tcctagttga acatacagaa 180

ataaatgtct aaaacagcac ctcgatttct gtctataaca ggactaagtt cactgtgatc 240
ttaaataagc ttggctaaaa tgggacatga gtggaggtag tcacacttca gcgaagaaag 300
agaatctcct gtataatctc accaggagat tcaacgaatt ccaccacact ggactagtgg 360
atcccccggg ctgcaggaat tcgatatcaa gcttatcgat accgtcgacc tcgaggggg 420
gcccggtacc caattcgccc tatagtgagt cgtattacgc gcgctcactg gccgtcgttt 480
tacaacgtcg tgactgggaa aaccctggcg ttacccaact taatcgcctt gcagcacatc 540
ccccttcgc cagctggcgt aatagcgaan agcccgcacc gatcgccctt ncaacagttg 600
cgcagcctga atggcgaatg ggacgcgccc tgtagcggcg cattaaagcg cggcngggtg 660
tggnggntcc cccacgtgac cgntacactt ggcagcgcct tacgccggtc nttcgctttc 720
ttcccttcct ttctcgcacc gttcgccggg tttccccgnn agctnttaat cgggggnctc 780
cctttanggg tncnaattaa nggnttacng gaccttngan cccaaaaact ttgattaggg 840
ggaaggtccc cgaagggg 858

<210> 92
<211> 585
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(585)
<223> n = A,T,C or G

<400> 92
gttgaatctc ctggtgagat tatacaggag attctctttc ttcgctgaag tgtgactacc 60
tccacttcatg tcccatttta gccaagctta tttaagatca cagtgaactt agtcctgtta 120
tagacgagaa tcgaggtgct gttttagaca tttatttctg tatgttcaac taggatcaga 180
atattacaga aaagcatggc ttgaataagg aaatgacaat ttttttcact tatctgatca 240
gaacaaatgt ttattaagca tcagaaactc tgccaacact gaggatgtaa agatcaataa 300
aaaaaataat aatcatnann naaanannan nngaagggcg gccgccaccg cggtggagct 360
ccagcttttg ttcccttttag tgagggttaa ttgcgcgctt ggcgttaatc atggtcatag 420
ctgtttcctg tgtgaaattg ttatccggct cacaattccn cncaacatac gagccgggaa 480
gcntnangtg taaaagcctg ggggtgccta attgagtgag ctnactcaca ttaattgngt 540
tgcgctccac ttgcccgctt ttccantccg ggaaacctgt tcgnc 585

<210> 93
<211> 567
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(567)
<223> n = A,T,C or G

<400> 93
cggcagtgtt gctgtctgcg tgtccacctt ggaatctggc tgaactggct gggaggacca 60
agactgcggc tggggtgggc anggaaggga accgggggct gctgtgaagg atcttggaac 120
ttcccctgtac ccaccttccc cttgcttcat gtttgtanag gaaccttgtg ccggccaagc 180
ccagtttcct tgtgtgatac actaatgtat ttgcttttt tgggaaatan anaaaaatca 240
attaaattgc tantgtttct ttgaannnnn nnnnnnnnnn nnnnnnnggg ggggncgccc 300
ccncggngga aacncccccc tttgttcccc ttaattgaaa ggttaattng cncncntggc 360
gttaancent gggccaaanc tngttnccng tgntgaaatt gttnatcccc tcccaaattc 420
ccccccnncc ttccaaaccc ggaaancctn annntgttna ancccggggg gttgcctaan 480
ngnaattnaa ccnaaccccc ntttaaatng nntttgcncn ccacnngccc cnctttccca 540

nttcggggaa aaccctntcc gtgccca 567

<210> 94
<211> 620
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(620)
<223> n = A,T,C or G

<400> 94
actagtcaaa aatgctaaaa taatttggga gaaaatattt tttaagtagt gttatagttt 60
catgtttatc ttttattatg ttttgtgaag ttgtgtcttt tcactaatta cctatactat 120
gccaatattt ccttatatct atccataaca tttatactac atttgtaana naatatgcac 180
gtgaaactta acactttata aggtaaaaat gaggtttcca anatttaata atctgatcaa 240
gttcttgtta tttccaaata gaatggactt ggtctgttaa gggctaagga gaagaggaag 300
ataaggttaa aagttgttaa tgaccaaaca ttctaaaaga aatgcaaaaa aaaagtttat 360
tttcaagcct tcgaactatt taaggaaagc aaaatcattt cctaaatgca tatcatttgt 420
gagaatttct cattaatatc ctgaatcatt catttcacta aggctcatgt tnactccgat 480
atgtctctaa gaaagtacta tttcatggtc caaacctggt tgccatantt gggtaaaggc 540
tttcccttaa gtgtgaaant atttaaaatg aaatttttcct ctttttaaaa attctttana 600
agggttaagg gtgttgggga 620

<210> 95
<211> 470
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(470)
<223> n = A,T,C or G

<400> 95
ctcgaccttc tctgcacagc ggatgaaccc tgagcagctg aagaccagaa aagccactat 60
nactttntgc ttaattcang agcttacang attcttcaaa gagtgngtcc agcatccttt 120
gaaacatgag ttcttaccag cagaagcaga cctttacccc accacctcag cttcaacagc 180
agcaggtgaa acaacccatc cagcctccac ctnaggaaat atttgttccc acaaccaagg 240
agccatgcca ctcaaaggtt ccacaacctg naaacacaaa nattccagag ccaggctgta 300
ccaaggtccc tgagccaggg ctgtaccaan gtccctgagc caggttgtac caangtccct 360
gagccaggat gtaccaaggt ccctgancca ggttgtccaa ggtccctgag ccaggctaca 420
ccaagggcct gngccaggca gcatcaangt ccctgaccaa ggcttatcaa 470

<210> 96
<211> 660
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(660)
<223> n = A,T,C or G

<400> 96
ttttttttt ttttttttt ggaattaaaa gcaatttaat gagggcagag caggaaacat 60
gcatttcttt tcattcgaat cttcagatga accctgagca gccgaagacc agaaaagcca 120
tgaagacttt ctgcttaatt caggggctta caggattctt cagagtgtgt gtgaacaaaa 180
gctttatagt acgtattttt aggatacaaa taagagagag actatggctt ggggtgagaa 240
tgtactgatt acaaggtcta cagacaatta agacacagaa acagatggga agagggtgnc 300
cagcatctgg nggttggctt ctcaagggct tgtctgtgca ccaaattact tctgcttggn 360
cttctgctga gctgggcctg gagtgaccgt tgaaggacat ggctctggta cctttgtgta 420
gcctgncaca ggaactttgg tgtatccttg ctcaggaact ttgatggcac ctggctcagg 480
aaacttgatg aagccttggt caagggacct tgatgcttgc tggctcaggg accttggngn 540
ancctgggct canggacctt tgncncaacc ttggcttcaa gggacccttg gnacatcctg 600
gcnnagggac ccttgggncc aaccctgggc ttnagggacc ctttggntnc nanccttggc 660

<210> 97
<211> 441
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(441)
<223> n = A,T,C or G

<400> 97
gggaccatac anagtattcc tctcttcaca ccaggaccag ccactgttgc agcatgagtt 60
cccagcagca gaagcagccc tgcatcccac cccctcagct tcagcagcag caggtgaaac 120
agccttgcca gcctccacct caggaaccat gcatccccaa aaccaaggag ccctgccacc 180
ccaaggtgcc tgagccctgc caccccaaag tgcctgagcc ctgccagccc aaggttccag 240
agccatgcca ccccaaggtg cctgagccct gcccttcaat agtcactcca gcaccagccc 300
agcagaanac caagcagaag taatgtggtc cacagccatg cccttgagga gccggccacc 360
agatgctgaa tcccctatcc cattctgtgt atgagtccca tttgccttgc aattagcatt 420
ctgtctcccc caaaaaaaaa a 441

<210> 98
<211> 600
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(600)
<223> n = A,T,C or G

<400> 98
gtattcctct cttcacacca ggaccagcca ctgttgcagc atgagttccc agcagcagaa 60
gcagccctgc atcccacccc ctcagcttca gcagcagcag gtgaaacagc cttgccagcc 120
tccacctcag gaaccatgca tccccaaaac caaggagccc tgccacccca aggtgcctga 180
gccctgccac cccaaagtgc ctgagccctg ccagcccaag gttccagagc catgccaccc 240
caaggtgcct gagccctgcc cttcaatagt cactccagca ccagcccagc agaanaccaa 300
gcagaagtaa tgtggtccac agccatgccc ttgaggagcc ggccaccana tgctgaatcc 360
cctatcccat tctgtgtatg agtcccattt gccttgcaat tagcattctg tctccccaa 420
aaaagaatgt gctatgaagc tttctttcct acacactctg agtctctgaa tgaagctgaa 480
ggtcttaant acaganctag ttttcagctg ctcagaattc tctgaagaaa agatttaaga 540
tgaaaggcaa atgattcagc tccttattac cccattaaat tcnctttcaa ttccaaaaaa 600

<210> 99
<211> 667
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G

<400> 99
actagtgact gagttcctgg caaagaaatt tgacctggac cagttgataa ctcatgtttt 60
accatttaaa aaaatcagtg aaggatttga gctgctcaat tcaggacaaa gcattcgaac 120
ggtcctgacg ttttgagatc caaagtggca ggaggtctgt gttgtcatgg tgaactggag 180
tttctcttgt gagagttccc tcatctgaaa tcatgtatct gtctcacaaa tacaagcata 240
agtagaagat ttgttgaaga catagaaccc ttataaagaa ttattaacct ttataaacat 300
ttaaagtctt gtgagcacct gggaattagt ataataacaa tgttnatatt tttgatttac 360
attttgtaag gctataattg tatcttttaa gaaaacatac cttggatttc tatgttgaaa 420
tggagatttt taagagtttt aaccagcngc tgcagatata ttactcaaaa cagatatagc 480
gtataaagat atagtaaatg catctcctag agtaatattc acttaacaca ttggaaacta 540
ttatttttta gatttgaata tnaatgttat tttttaaaca cttgttatga gttacttggg 600
attacatttt gaaatcagtt cattccatga tgcanattac tgggattaga ttaagaaaga 660
cggaaaa 667

<210> 100
<211> 583
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(583)
<223> n = A,T,C or G

<400> 100
gttttgtttg taagatgatc acagtcatgt tacactgatc taaaggacat atatataacc 60
ctttaaaaaa aaaatcactg cctcattctt atttcaagat gaatttctat acagactaga 120
tgtttttctg aagatcaatt agacattttg aaaatgattt aaagtgtttt ccttaatgtt 180
ctctgaaaac aagtttcttt tgtagtttta accaaaaaag tgccctttt gtcactggat 240
tctcctagca ttcatgattt ttttttcata caatgaaatt aaaattgcta aaatcatgga 300
ctggctttct ggttggattt caggtaagat gtgtttaagg ccagagcttt tctcagtatt 360
tgatttttt ccccaatatt tgatttttta aaaatataca catnggtgct gcatttatat 420
ctgctggttt aaaattctgt catatttcac ttctagcctt ttagttatgg caaatcatat 480
tttactttta cttaaagcat ttggtnattt ggantatctg gttctannct aaaaaaanta 540
attctatnaa ttgaantttt ggtactcnnc catatttgga tcc 583

<210> 101
<211> 592
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(592)
<223> n = A,T,C or G

<400> 101
gtggagacgt acaaagagca gccgctcaag acacctggga agaaaaagaa aggcaagccc 60
gggaaacgca aggagcagga aaagaaaaaa cggcgaactc gctctgcctg gttagactct 120
ggagtgactg ggagtgggct agaaggggac cacctgtctg acacctccac aacgtcgctg 180
gagctcgatt cacggaggca ttgaaatttt cagcaganac cttccaagga catattgcag 240
gattctgtaa tagtgaacat atggaaagta ttagaaatat ttattgtctg taaatactgt 300
aaatgcattg gaataaaact gtctccccca ttgctctatg aaactgcaca ttggtcattg 360
tgaatatttt ttttttgcc aaggctaatc caattattat tatcacattt accataattt 420
attttgtcca ttgatgtatt tattttgtaa atgtatcttg gtgctgctga atttctatat 480
tttttgtaca taatgcnttt anatatacct atcaagtttg ttgataaatg acncaatgaa 540
gtgncncnan ttggnggttg aatttaatga atgcctaatt ttattatccc aa 592

<210> 102
<211> 587
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(587)
<223> n = A,T,C or G

<400> 102
cgtcctaagc acttagacta catcagggaa gaacacagac cacatccctg tcctcatgcg 60
gcttatgttt tctggaagaa agtggagacc nagtccttgg ctttagggct ccccggctgg 120
gggctgtgca ntccggtcag ggcgggaagg gaaatgcacc gctgcatgtg aacttacagc 180
ccaggcggat gccccttccc ttagcactac ctggcctcct gcatcccctc gcctcatgtt 240
cctcccacct tcaaanaatg aanaacccca tgggcccagc cccttgcccc ggggaaccaa 300
ggcagccttc caaaactcag gggctgaagc anactattag ggcaggggct gactttgggt 360
gacactgccc attcccctct agggcagctc angtcacccn ggnctcttga acccagcctg 420
ttcctttgaa aaagggcaaa actgaaaagg gcttttccta naaaaagaaa aaccagggaa 480
ctttgccagg gcttcnntnt taccaaaacn ncttctcnng gatttttaat tccccattng 540
gcctccactt accnggggcn atgccccaaa attaanaatt tcccatc 587

<210> 103
<211> 496
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(496)
<223> n = A,T,C or G

<400> 103
anaggactgg ccctacntgc tctctctcgt cctacctatc aatgcccaac atggcagaac 60
ctgcanccct tggncactgc anatggaaac ctctcagtgt cttgacatca ccctacccnt 120
gcggtgggtc tccaccacaa ccactttgac tctgtggtcc ctgnanggtg gnttctcctg 180
actggcagga tggaccttan ccnacatatc cctctgttcc ctctgctnag anaaagaatt 240
cccttaacat gatataatcc acccatgcaa ntngctactg gcccagctac catttaccat 300
ttgcctacag aatttcattc agtctacact ttggcattct ctctggcgat agagtgtggc 360
tgggctgacc gcaaaaggtg ccttacacac tggcccccac cctcaaccgt tgacncatca 420
gangcttgcc tcctcctttct gattnncccc catgttggat atcagggtgc tcnagggatt 480
ggaaaagaaa caaaac 496

<210> 104
<211> 575
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(575)
<223> n = A,T,C or G

<400> 104
gcacctgctc tcaatccnnc tctcaccatg atcctccgcc tgcanaaact cctctgccaa 60
ctatggangt ggtttcnggg gtggctcttg ccaactggga agaagccgtg gtgtctctac 120
ctgttcaact cngtttgtgt ctgggggatc aactnggggc tatggaagcg gctnaactgt 180
tgttttggtg gaagggctgg taattggctt tgggaagtng cttatngaag ttggcctngg 240
gaagttgcta ttgaaagtng ccntggaagt ngntttggtg gggggttttg ctggtggcct 300
ttgttnaatt tgggtgcttt gtnaatggcg gccccctcnc ctgggcaatg aaaaaaatca 360
ccnatgcngn aaacctcnac nnaacagcct gggcttcccc cacctcgaaa aaagttgctc 420
cccccccaaa aaaggncaan cccctcaann tggaangttg aaaaaatcct cgaatgggga 480
ncccnaaaac aaaaancccc ccntttcccn gnaanggggg aaataccncc cccccactta 540
cnaaaaccct tntaaaaaac cccccgggaa aaaaa 575

<210> 105
<211> 619
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(619)
<223> n = A,T,C or G

<400> 105
cactagtagg atagaaacac tgtgtcccga gagtaaggag agaagctact attgattaga 60
gcctaaccca ggttaactgc aagaagaggc gggatacttt cagctttcca tgtaactgta 120
tgcataaagc caatgtagtc cagtttctaa gatcatgttc caagctaact gaatcccact 180
tcaatacaca ctcatgaact cctgatggaa caataacagg cccaagcctg tggtatgatg 240
tgcacacttg ctagactcan aaaaaatact actctcataa atgggtggga gtattttggt 300
gacaacctac tttgcttggc tgagtgaagg aatgatattc atatattcat ttattccatg 360
gacatttagt tagtgctttt tatataccag gcatgatgct gagtgacact cttgtgtata 420
tttccaaatt tttgtacagt cgctgcacat atttgaaatc atatattaag acttccaaaa 480
aatgaagtcc ctggtttttc atggcaactt gatcagtaaa ggattcncct ctgtttggta 540
cttaaaacat ctactatatn gttnanatga aattcctttt ccccncctcc cgaaaaaana 600
aagtggtggg gaaaaaaaa 619

<210> 106
<211> 506
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(506)
<223> n = A,T,C or G

<400> 106
cattggtnct ttcatttgct ntggaagtgt nnatctctaa cagtggacaa agttcccngt 60
gccttaaact ctgtnacact tttgggaant gaaaanttng tantatgata ggttattctg 120
angtanagat gttctggata ccattanatn tgccccngt gtcagaggct catattgtgt 180
tatgtaaatg gtatntcatt cgctactatn antcaattng aaatanggtc tttgggttat 240
gaatantnng cagcncanct nanangctgt ctgtngtatt cattgtggtc atagcacctc 300
acancattgt aacctcnatc nagtgagaca nactagnaan ttcctagtga tggctcanga 360
ttccaaatgg nctcatntcn aatgtttaaa agttanttaa gtgtaagaaa tacagactgg 420
atgttccacc aactagtacc tgtaatgacn ggcctgtccc aacacatctc ccttttccat 480
gactgtggta ncccgcatcg gaaaaa 506

<210> 107
<211> 452
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(452)
<223> n = A,T,C or G

<400> 107
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tcttttgaag catagataat attgtttggt aaatgtttct tttgtttggt aaatgtttct 120
tttaaagacc ctcctattct ataaaactct gcatgtagag gcttgtttac ctttctctct 180
ctaaggttta caataggagt ggtgatttga aaaatataaa attatgagat tggttttcct 240
gtggcataaa ttgcatcact gtatcatttt cttttttaac cggtaagant ttcagtttgt 300
tggaaagtaa ctgtganaac ccagtttccc gtccatctcc cttagggact acccatagaa 360
catgaaaagg tccccacnga agcaagaaga taagtctttc atggctgctg gttgcttaaa 420
ccactttaaa accaaaaaat tccccttgga aa 452

<210> 108
<211> 502
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 108
atcttcttcc cttaattagt tnttatttat ntattaaatt ttattgcatg tcctggcaaa 60
caaaaagaga ttgtagattg gcttctggct ccccaaaagc ccataacaga aagtaccaca 120
agaccncaac tgaagcttaa aaaatctatc acatgtataa tacctttnga agaacattaa 180
tanagcatat aaaacttta acatntgctt aatgttgtnc aattataaaa ntaatngaaa 240
aaaatgtccc tttaacatnc aatatcccac atagtgttat ttnaggggat taccnngnaa 300
naaaaaaagg gtagaaggga tttaatgaaa actctgcttn ccatttctgt ttanaaacgt 360
ctccagaaca aaaacttntc aantctttca gctaaccgca tttgagctna ggccactcaa 420
aaactccatt agncccactt tctaanggtc tctanagctt actaancctt ttgacccctt 480
accctggnta ctcctgcccc ca 502

<210> 109
<211> 1308

<212> DNA
<213> Homo sapien

<400> 109
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tttgatcttt tcaaagagct gaagaaaaca aatgatggca acatcttctt ttcccctgtg 120
ggcatcttga ctgcaattgg catggtcctc ctggggaccc gaggagccac cgcttcccag 180
ttggaggagg tgtttcactc tgaaaaagag acgaagagct caagaataaa ggctgaagaa 240
aaagaggtga ttgagaacac agaagcagta catcaacaat tccaaaagtt tttgactgaa 300
ataagcaaac tcactaatga ttatgaactg aacataacca acaggctgtt tggagaaaaa 360
acatacctct tccttcaaaa atacttagat tatgttgaaa aatattatca tgcatcttcg 420
gaacctgttg attttgtaaa tgcagccgat gaaagtcgaa agaagattaa ttcctgggtt 480
gaaagcaaaa caaatgaaaa aatcaaggac ttgttcccag atggctctat tagtagctct 540
accaagctgg tgctggtgaa catggtttat tttaaagggc aatgggacag ggagtttaag 600
aaagaaaata ctaaggaaga gaaattttgg atgaataaga gcacaagtaa atctgtacag 660
atgatgacac agagccattc ctttagcttc actttcctgg aggacttgca ggccaaaatt 720
ctagggattc catataaaaa caacgaccta agcatgtttg tgcttctgcc caacgacatc 780
gatggcctgg agaagataat agataaaata agtcctgaga aattggtaga gtggactagt 840
ccagggcata tggaagaaag aaaggtgaat ctgcacttgc cccggtttga ggtggaggac 900
agttacgatc tagaggcggt cctggctgcc atggggatgg gcgatgcctt cagtgagcac 960
aaagccgact actcgggaat gtcgtcaggc tccgggttgt acgcccagaa gttcctgcac 1020
agttcctttg tggcagtaac tgaggaaggc accgaggctg cagctgccac tggcataggc 1080
tttactgtca catccgcccc aggtcatgaa aatgttcact gcaatcatcc cttcctgttc 1140
ttcatcaggc acaatgaatc caacagcatc ctcttcttcg gcagattttc ttctccttaa 1200
gatgatcgtt gccatggcat tgctgctttt agcaaaaaac aactaccagt gttactcata 1260
tgattatgaa aatcgtccat tcttttaaat ggtggctcac ttgcattt 1308

<210> 110
<211> 391
<212> PRT
<213> Homo sapien

<400> 110
Met Asp Ser Leu Gly Ala Val Ser Thr Arg Leu Gly Phe Asp Leu Phe
1 5 10 15
Lys Glu Leu Lys Lys Thr Asn Asp Gly Asn Ile Phe Phe Ser Pro Val
20 25 30
Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala
35 40 45
Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
50 55 60
Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Ile Glu Asn Thr Glu
65 70 75 80
Ala Val His Gln Gln Phe Gln Lys Phe Leu Thr Glu Ile Ser Lys Leu
85 90 95
Thr Asn Asp Tyr Glu Leu Asn Ile Thr Asn Arg Leu Phe Gly Glu Lys
100 105 110
Thr Tyr Leu Phe Leu Gln Lys Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr
115 120 125
His Ala Ser Leu Glu Pro Val Asp Phe Val Asn Ala Ala Asp Glu Ser
130 135 140
Arg Lys Lys Ile Asn Ser Trp Val Glu Ser Lys Thr Asn Glu Lys Ile
145 150 155 160
Lys Asp L u Phe Pro Asp Gly Ser Ile Ser Ser Ser Thr Lys Leu Val
165 170 175

```
Leu Val Asn Met Val Tyr Phe Lys Gly Gln Trp Asp Arg Glu Phe Lys
            180                 185                 190
Lys Glu Asn Thr Lys Glu Glu Lys Phe Trp Met Asn Lys Ser Thr Ser
        195                 200                 205
Lys Ser Val Gln Met Met Thr Gln Ser His Ser Phe Ser Phe Thr Phe
    210                 215                 220
Leu Glu Asp Leu Gln Ala Lys Ile Leu Gly Ile Pro Tyr Lys Asn Asn
225                 230                 235                 240
Asp Leu Ser Met Phe Val Leu Leu Pro Asn Asp Ile Asp Gly Leu Glu
                245                 250                 255
Lys Ile Ile Asp Lys Ile Ser Pro Glu Lys Leu Val Glu Trp Thr Ser
            260                 265                 270
Pro Gly His Met Glu Glu Arg Lys Val Asn Leu His Leu Pro Arg Phe
        275                 280                 285
Glu Val Glu Asp Ser Tyr Asp Leu Glu Ala Val Leu Ala Ala Met Gly
    290                 295                 300
Met Gly Asp Ala Phe Ser Glu His Lys Ala Asp Tyr Ser Gly Met Ser
305                 310                 315                 320
Ser Gly Ser Gly Leu Tyr Ala Gln Lys Phe Leu His Ser Ser Phe Val
                325                 330                 335
Ala Val Thr Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Gly Ile Gly
            340                 345                 350
Phe Thr Val Thr Ser Ala Pro Gly His Glu Asn Val His Cys Asn His
        355                 360                 365
Pro Phe Leu Phe Phe Ile Arg His Asn Glu Ser Asn Ser Ile Leu Phe
    370                 375                 380
Phe Gly Arg Phe Ser Ser Pro
385                 390
```

<210> 111
<211> 1419
<212> DNA
<213> Homo sapien

<400> 111

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ggagaactat aaattaagga tcccagctac ttaattgact tatgcttcct agttcgttgc      60
ccagccacca ccgtctctcc aaaaacccga ggtctcgcta aaatcatcat ggattcactt     120
ggcgccgtca gcactcgact tgggtttgat cttttcaaag agctgaagaa aacaaatgat     180
ggcaacatct tcttttcccc tgtgggcatc ttgactgcaa ttggcatggt cctcctgggg     240
acccgaggag ccaccgcttc ccagttggag gaggtgtttc actctgaaaa agagacgaag     300
agctcaagaa taaaggctga agaaaaagag gtggtaagaa taaaggctga aggaaaagag     360
attgagaaca cagaagcagt acatcaacaa ttccaaaagt ttttgactga aataagcaaa     420
ctcactaatg attatgaact gaacataacc aacaggctgt ttggagaaaa aacatacctc     480
ttccttcaaa aatacttaga ttatgttgaa aaatattatc atgcatctct ggaacctgtt     540
gattttgtaa atgcagccga tgaaagtcga aagaagatta attcctgggt tgaaagcaaa     600
acaaatgaaa aaatcaagga cttgttccca gatggctcta ttagtagctc taccaagctg     660
gtgctggtga acatggttta ttttaaaggg caatgggaca gggagtttaa gaaagaaaat     720
actaaggaag agaaattttg gatgaataag agcacaagta aatctgtaca gatgatgaca     780
cagagccatt cctttagctt cactttcctg gaggacttgc aggccaaaat tctagggatt     840
ccatataaaa acaacgacct aagcatgttt gtgcttctgc ccaacgacat cgatggcctg     900
gagaagataa tagataaaat aagtcctgag aaattggtag agtggactag tccagggcat     960
atggaagaaa gaaaggtgaa tctgcacttg ccccggtttg aggtggagga cagttacgat    1020
ctagaggcgg tcctggctgc catggggatg ggcgatgcct tcagtgagca caaagccgac    1080
tactcgggaa tgtcgtcagg ctccgggttg tacgcccaga agttcctgca cagttccttt    1140
gtggcagtaa ctgaggaagg caccgaggct gcagctgcca ctggcatagg ctttactgtc    1200
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acatccgccc caggtcatga aaatgttcac tgcaatcatc ccttcctgtt cttcatcagg 1260
cacaatgaat ccaacagcat cctcttcttc ggcagatttt cttctcctta agatgatcgt 1320
tgccatggca ttgctgcttt tagcaaaaaa caactaccag tgttactcat atgattatga 1380
aaatcgtcca ttcttttaaa tggtggctca cttgcattt 1419

<210> 112
<211> 400
<212> PRT
<213> Homo sapien

<400> 112

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Met Asp Ser Leu Gly Ala Val Ser Thr Arg Leu Gly Phe Asp Leu Phe
 1               5                  10                  15
Lys Glu Leu Lys Lys Thr Asn Asp Gly Asn Ile Phe Phe Ser Pro Val
            20                  25                  30
Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala
        35                  40                  45
Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
    50                  55                  60
Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Val Arg Ile Lys Ala
65                  70                  75                  80
Glu Gly Lys Glu Ile Glu Asn Thr Glu Ala Val His Gln Gln Phe Gln
                85                  90                  95
Lys Phe Leu Thr Glu Ile Ser Lys Leu Thr Asn Asp Tyr Glu Leu Asn
            100                 105                 110
Ile Thr Asn Arg Leu Phe Gly Glu Lys Thr Tyr Leu Phe Leu Gln Lys
        115                 120                 125
Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr His Ala Ser Leu Glu Pro Val
    130                 135                 140
Asp Phe Val Asn Ala Ala Asp Glu Ser Arg Lys Lys Ile Asn Ser Trp
145                 150                 155                 160
Val Glu Ser Lys Thr Asn Glu Lys Ile Lys Asp Leu Phe Pro Asp Gly
                165                 170                 175
Ser Ile Ser Ser Ser Thr Lys Leu Val Leu Val Asn Met Val Tyr Phe
            180                 185                 190
Lys Gly Gln Trp Asp Arg Glu Phe Lys Lys Glu Asn Thr Lys Glu Glu
        195                 200                 205
Lys Phe Trp Met Asn Lys Ser Thr Ser Lys Ser Val Gln Met Met Thr
    210                 215                 220
Gln Ser His Ser Phe Ser Phe Thr Phe Leu Glu Asp Leu Gln Ala Lys
225                 230                 235                 240
Ile Leu Gly Ile Pro Tyr Lys Asn Asn Asp Leu Ser Met Phe Val Leu
                245                 250                 255
Leu Pro Asn Asp Ile Asp Gly Leu Glu Lys Ile Ile Asp Lys Ile Ser
            260                 265                 270
Pro Glu Lys Leu Val Glu Trp Thr Ser Pro Gly His Met Glu Glu Arg
        275                 280                 285
Lys Val Asn Leu His Leu Pro Arg Phe Glu Val Glu Asp Ser Tyr Asp
    290                 295                 300
Leu Glu Ala Val Leu Ala Ala Met Gly Met Gly Asp Ala Phe Ser Glu
305                 310                 315                 320
His Lys Ala Asp Tyr Ser Gly Met Ser Ser Gly Ser Gly Leu Tyr Ala
                325                 330                 335
Gln Lys Phe Leu His Ser Ser Phe Val Ala Val Thr Glu Glu Gly Thr
            340                 345                 350
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Glu Ala Ala Ala Ala Thr Gly Ile Gly Phe Thr Val Thr Ser Ala Pro
        355                 360                 365
Gly His Glu Asn Val His Cys Asn His Pro Phe Leu Phe Phe Ile Arg
    370                 375                 380
His Asn Glu Ser Asn Ser Ile Leu Phe Phe Gly Arg Phe Ser Ser Pro
385                 390                 395                 400
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<210> 113
<211> 957
<212> DNA
<213> Homo sapien

<400> 113

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ctcgaccttc tctgcacagc ggatgaaccc tgagcagctg aagaccagaa aagccactat      60
gacttttctgc ttaattcagg agcttacagg attcttcaaa gagtgtgtcc agcatccttt     120
gaaacatgag ttcttaccag cagaagcaga cctttacccc accacctcag cttcaacagc     180
agcaggtgaa acaacccagc cagcctccac ctcaggaaat atttgttccc acaaccaagg     240
agccatgcca ctcaaaggtt ccacaacctg gaaacacaaa gattccagag ccaggctgta     300
ccaaggtccc tgagccaggc tgtaccaagg tccctgagcc aggttgtacc aaggtccctg     360
agccaggatg taccaaggtc cctgagccag gttgtaccaa ggtccctgag ccaggctaca     420
ccaaggtccc tgagccaggc agcatcaagg tccctgacca aggcttcatc aagtttcctg     480
agccaggtgc catcaaagtt cctgagcaag gatacaccaa agttcctgtg ccaggctaca     540
caaaggtacc agagccatgt ccttcaacgg tcactccagg cccagctcag cagaagacca     600
agcagaagta atttggtgca cagacaagcc cttgagaagc caaccaccag atgctggaca     660
ccctctttcc atctgtttct gtgtcttaat tgtctgtaga ccttgtaatc agtacattct     720
caccccaagc catagtctct ctctttatttg tatcctaaaa atacggtact ataaagcttt     780
tgttcacaca cactctgaag aatcctgtaa gccccctgaat taagcagaaa gtcttcatgg     840
ctttttctggt ctttggctgc tcagggttca tctgaagatt cgaatgaaaa gaaatgcatg     900
tttcctgctc tgccctcatt aaattgcttt taattccaaa aaaaaaaaaa aaaaaaa         957
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<210> 114
<211> 161
<212> PRT
<213> Homo sapien

<400> 114

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Met Ser Ser Tyr Gln Gln Lys Gln Thr Phe Thr Pro Pro Pro Gln Leu
 1               5                  10                  15
Gln Gln Gln Gln Val Lys Gln Pro Ser Gln Pro Pro Pro Gln Glu Ile
            20                  25                  30
Phe Val Pro Thr Thr Lys Glu Pro Cys His Ser Lys Val Pro Gln Pro
        35                  40                  45
Gly Asn Thr Lys Ile Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
    50                  55                  60
Gly Cys Thr Lys Val Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
65                  70                  75                  80
Gly Cys Thr Lys Val Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
                85                  90                  95
Gly Tyr Thr Lys Val Pro Glu Pro Gly Ser Ile Lys Val Pro Asp Gln
            100                 105                 110
Gly Phe Ile Lys Phe Pro Glu Pro Gly Ala Ile Lys Val Pro Glu Gln
        115                 120                 125
Gly Tyr Thr Lys Val Pro Val Pro Gly Tyr Thr Lys Val Pro Glu Pro
    130                 135                 140
Cys Pro Ser Thr Val Thr Pro Gly Pro Ala Gln Gln Lys Thr Lys Gln
```

145 150 155 160
Lys

<210> 115
<211> 506
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(506)
<223> n = A,T,C or G

<400> 115
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gccttaaact ctgtnacact tttgggaant gaaaanttng tantatgata ggttattctg 120
angtanagat gttctggata ccattanatn tgcccccngt gtcagaggct catattgtgt 180
tatgtaaatg gtatntcatt cgctactatn antcaattng aaatanggtc tttgggttat 240
gaatantnng cagcncanct nanangctgt ctgtngtatt cattgtggtc atagcaccta 300
acancattgt aacctcnatc nagtgagaca nactagnaan ttcctagtga tggctcanga 360
ttccaaatgg nctcatntcn aatgtttaaa agttanttaa gtgtaagaaa tacagactgg 420
atgttccacc aactagtacc tgtaatgacn ggcctgtccc aacacatctc cctttttcat 480
gactgtggta ncccgcatcg gaaaaa 506

<210> 116
<211> 3079
<212> DNA
<213> Homo sapien

<400> 116
ggatccccgg gtttcctaaa ccccccacag agtcctgccc aggccaaaga gcaaggaaaa 60
ggtcaaaggg cagaaaaaat gctgagttag gaggagctat ggaaggataa acctggcctt 120
aaagaggtca aagtggttta taggggggcgc tgagggcttc ccacattctc tggcctaaac 180
cttgcaggca gatctgccca gtgggctctg ggatagctgt gccttcccta acaaaaaaat 240
tgtgcacaaa aggatgaaac tctatttttcc ctctagcaca taaccaagaa tataaggcta 300
cagattgcct ttcccagagg gaaaaccctg cagcaacctg ctgcctggaa aagtgtaaga 360
gcagatcact ggggaatcgt ttgccccccg ctgatggaca gcttccccaa gctccaaggg 420
caggtgctca gcatgtaccg tactgggatg gttgtcaata ctcctggtcc tgtaagagtc 480
ccaggacact gccatgccaa tgcccccctca gttcctggca tcctttttgg gctgctcaca 540
gccccagcct ctatggtgaa gacatacttg ctagcagcgt caccaacttg ttgccaagag 600
atcagtgctc gaaggcaagg ttatttctaa ctgagcagag cctgccagga agaaagcgtt 660
tgcaccccac accactgtgc aggtgtgacc ggtgagctca cagctgcccc ccaggcatgc 720
ccagcccact taatcatcac agctcgacag ctctctcgcc cagcccagtt ctggaaggga 780
taaaaagggg catcaccgtt cctgggtaac agagccacct tctgcgtcct gctgagctct 840
gttctctcca gcacctccca acccactagt gcctggttct cttgctccac caggaacaag 900
ccaccatgtc tcgccagtca agtgtgtctt ccggagcggg gggcagtcgt agcttcagca 960
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agtggaccct gctgcaggag cagggcacca agactgtgag gcagaacctg gagccgttgt 1560
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gcctggactc agagctgaga aacatgcagg acctggtgga agacttcaag aacaagtatg 1680
aggatgaaat caacaagcgt accactgctg agaatgagtt tgtgatgctg aagaaggatg 1740
tagatgctgc ctacatgaac aaggtggagc tggaggccaa ggttgatgca ctgatggatg 1800
agattaactt catgaagatg ttctttgatg cggagctgtc ccagatgcag acgcatgtct 1860
ctgacacctc agtggtcctc tccatggaca acaaccgcaa cctggacctg gatagcatca 1920
tcgctgaggt caaggcccag tatgaggaga ttgccaaccg cagccggaca gaagccgagt 1980
cctggtatca gaccaagtat gaggagctgc agcagacagc tggccggcat ggcgatgacc 2040
tccgcaacac caagcatgag atctctgaga tgaaccggat gatccagagg ctgagagccg 2100
agattgacaa tgtcaagaaa cagtgcgcca atctgcagaa cgccattgcg gatgccgagc 2160
agcgtgggga gctggccctc aaggatgcca ggaacaagct ggccgagctg gaggaggccc 2220
tgcagaaggc caagcaggac atggccggc tgctgcgtga gtaccaggag ctcatgaaca 2280
ccaagctggc cctggacgtg gagatcgcca cttaccgcaa gctgctggag ggcgaggaat 2340
gcagactcag tggagaagga gttggaccag tcaacatctc tgttgtcaca agcagtgttt 2400
cctctggata tggcagtggc agtggctatg gcggtggcct cggtggaggt cttggcggcg 2460
gcctcggtgg aggttttgcc ggaggtagca gtggaagcta ctactccagc agcagtgggg 2520
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gagggctggg ggtgggcttt ggcagtggcg ggggtagcag ctccagcgtc aaattttgtct 2640
ccaccacctc ctcctcccgg aagagcttca agagctaaga acctgctgca agtcactgcc 2700
ttccaagtgc agcaacccag cccatggaga ttgcctcttc taggcagttg ctcaagccat 2760
gttttatcct tttctggaga gtagtctaga tcaagccaat tgcagaacca cattctttgg 2820
ttcccaggag agccccattc ccagcccctg gtctcccgtg ccgcagtttt atattctgct 2880
tcaaatcagc cttcaggttt cccacagcat ggcccctgct gacacgagaa cccaaagttt 2940
tcccaaatct aaatcatcaa aacagaatcc ccacccccaat cccaaatttt gttttggttc 3000
taactacctc cagaatgtgt tcaataaaat gttttataat ataagctggt gtgcagaatt 3060
gttttttttt tctacccaa 3079

<210> 117
<211> 6921
<212> DNA
<213> Homo sapien

<400> 117
gaattctgac tgtccactca aaacttctat tccgatcaaa gctatctgtg actacagaca 60
aattgagata accatttaca aagacgatga atgtgttttg gcgaataact ctcatcgtgc 120
taaatggaag gtcattagtc ctactgggaa tgaggctatg gtcccatctg tgtgcttcac 180
cgttcctcca ccaaacaaag aagcggtgga ccttgccaac agaattgagc aacagtatca 240
gaatgtcctg actctttggc atgagtctca cataaacatg aagagtgtag tatcctggca 300
ttatctcatc aatgaaattg atagaattcg agctagcaat gtggcttcaa taaagacaat 360
gctacctggt gaacatcagc aagttctaag taatctacaa tctcgttttg aagatttttt 420
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ggcactag 8948

<210> 120
<211> 587
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(587)
<223> n = A,T,C or G

<400> 120
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ccaggcggat gccccttccc ttagcactac ctggcctcct gcatcccctc gcctcatgtt 240
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gacactgccc attccctctc agggcagctc angtcacccn ggnctcttga acccagcctg 420
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gcctccactt accnggggcn atgccccaaa attaanaatt tcccatc 587

<210> 121
<211> 619
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(619)
<223> n = A,T,C or G

<400> 121
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tgcataaagc caatgtagtc cagtttctaa gatcatgttc caagctaact gaatcccact 180
tcaatacaca ctcatgaact cctgatggaa caataacagg cccaagcctg tggtatgatg 240
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gacaacctac tttgcttggc tgagtgaagg aatgatattc atatattcat ttattccatg 360
gacatttagt tagtgctttt tatataccag gcatgatgct gagtgacact cttgtgtata 420
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aatgaagtcc ctggtttttc atggcaactt gatcagtaaa ggattcncct ctgtttggta 540
cttaaaacat ctactatatn gttnanatga aattcctttt ccccncctcc cgaaaaaana 600
aagtggtggg gaaaaaaaa 619

<210> 122
<211> 1475
<212> DNA
<213> Homo sapien

<400> 122
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tcgtgagcga ctccaaaggc agcaatgaac ttcatcaagt tccatcgaac tgtgactgtc 180
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<210> 123
<211> 2294
<212> DNA
<213> Homo sapien

<400> 123
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aaaggcagca atgaacttca tcaagttcca tcgaactgtg actgtctaaa tggaggaaca 180
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cataattact gcaggaaccc agacaaccgg aggcgaccct ggtgctatgt gcaggtgggc 480
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<210> 124
<211> 956
<212> DNA
<213> Homo sapien

<400> 124
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<210> 125
<211> 486
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(486)
<223> n = A,T,C or G

<400> 125
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gcattttagg acattatggc agctttagaa ggctgtcttg tttctagcca agggagagcc 360

agcgcaggtt ttggatacta gagaaagtca tttgcttgta ctattgccat tttagaaagc 420
tctgatgtga attcaaattt tacctctgtt actttaaagcc aacaatttta aggcagtagt 480
tttact 486

<210> 126
<211> 3552
<212> DNA
<213> Homo sapien

<400> 126
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ttgtaaataa at 3552

<210> 127
<211> 754
<212> DNA
<213> Homo sapien

<400> 127
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gccttttcaaa ggtcacacag aagtaagtga cagatccagg attcatatcc aagcattctg 120
gctctagtgt ccatgctttct caaccattat gacccaatat ttaaccaaat caatactgaa 180
ggacacgtga aatgtatccg gtatttttact attacaaaca aaaatccaat gaacattctt 240
gaagacatac acaaaaataa tggttacaat agaagttact ggaattgaaa ttttggttca 300
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cctttatggt tggatcatct tgtcattaaa gttcaggcgt tatctatcct gtaagtggca 480
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<210> 128
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<400> 134

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<210> 136
<211> 356
<212> DNA
<213> Homo sapien

<400> 136
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tgaccacaca aaacagaacc aggactggac tcagtggaac ccaagccatt caaatccgga 180
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tgaaggaaac tggaacccag aagcacaccc tcccctcatt caccatgagc atcatgagga 300
agaagagacc ccacattcta caagcacaat ccaggcaact cctagtagta caacgg 356

<210> 137
<211> 356
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(356)
<223> n = A,T,C or G

<400> 137
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ctatgtctcc cagcaaggac agaaactcag aaaaatcaat cttcttatcc tcattcttgt 180
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cgctaaggcc aaanttccag acanayggcc gggccggtnc nataggggan cccaacttgg 300
ggacccaaac tctggcgcgg aaacacangg gcataagctt gnttcctgtg gggaaa 356

<210> 138
<211> 353
<212> DNA
<213> Homo sapien

<400> 138
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aatgccagcc atcttggcat cctggcccct gagcaggctg cggtaagtag cgatctcctg 240
ctccagccgt gtctttatgt caagcagcat cttgtactcc tggttctgag cctccatctc 300
gcatcggagc tcactcagac ctcgsccgsg mssmcgctam gccgaattcc agc 353

<210> 139
<211> 371
<212> DNA
<213> Homo sapien

<400> 139
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agccttggaa aggtcactga aaaatcttca attggattat gttgaccttt accttattca 180
ttttccagtg tctgtaaagc caggtgagga agtgatccca aaagatgaaa atggaaaaat 240
actatttgac acagtggatc tctgtgccac gtgggaggcc gtggagaagt gtaaagatgc 300
aggattggac ctgcccgggc ggccgcttcga aagccgaatt ccagcacact ggcggccgtt 360
actagtggat c 371

<210> 140
<211> 370
<212> DNA
<213> Homo sapien

<400> 140
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aggagctgcc tgagtggtac tttctcttcc tggtaatcct ctggcccagc ctcatggcag 180
aatagaggta tttttaggct atttttgtaa tatggcttct ggtcaaaatc cctgtgtagc 240
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agttaacact caaaaaaaaa aaaaaacctg cccgggcggc cgctcgaaag ccgaattcca 360
gcacactggc 370

<210> 141
<211> 371
<212> DNA
<213> Homo sapien

<400> 141
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aaggagcttc agggtcctgg tactcctcca cagaatactc ggagtattca gagtactcat 180
catcctcagg gggtacccgc tcttcctcct ctgcatgaga gacgcggagc acaggcacag 240
catggagctg ggagccggca gtgtctgcag cataactagg gaggggtcgt gatccagatg 300
cgatgaactg gccctggcag gcacagtgct gactcatctc ttggcgacct gcccgggcgg 360
ccgctcgaag c 371

<210> 142
<211> 343
<212> DNA
<213> Homo sapien

<400> 142
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agagcagttt tgaaacactc ttttgtagaa tttgcaagcg gatgattgga tcgctatgag 180
gtcttcattg gaaacgggat acctttacat aaaaactaga cagtagcatt ctcagaaatt 240
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aacaccctt ttgtagaatc tacaggtgga catttagagt gct 343

<210> 143
<211> 354
<212> DNA
<213> Homo sapien

<400> 143
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gtggtggagt gtgtcatgaa caatgtcacc tgtactcgga tctatgaaaa agtagaataa 180
aaattccatc atcactttgg acaggagtta attaagagaa tgaccaagct cagttcaatg 240
agcaaatctc catactgttt ctttctttttt ttttttcatta ctgtgttcaa ttatctttat 300
cataaacatt ttacatgcag ctatttcaaa gtgtgttgga ttaattagga tcat 354

<210> 144
<211> 353
<212> DNA
<213> Homo sapien

<400> 144
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gaaaccatgc cccagagaag gttaagtgac ttcctctttta tggagccagt gttccaacct 300
aggtttgcct gataccagac ctgtggcccc acctccccatg caggtctctg tgg 353

<210> 145
<211> 371
<212> DNA
<213> Homo sapien

<400> 145
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attgccactg ttgatcacta gctttttctt ctgcccacac cttcttcgac tgttgactgc 180
aatgcaaact gcaagaatca aagccaaggc caagagggat gccaagatga tcagccattc 240

tggaatttgg ggtgtcctta taggaccaga ggttgtgttt gctccacctt cttgactccc 300
atgtgagacc tcggccgcga ccacgctaag ccgaattcca gcacactggc ggccgttac 360
tagtggatcc g 371

<210> 146
<211> 355
<212> DNA
<213> Homo sapien

<400> 146
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cgagagcaag ctctataaga ttcttcaagg tggggttggc atcccccaca tacggtggta 300
tggtcaggaa aaagactaca atgtactagt catggatctt ctgggaccta gcctc 355

<210> 147
<211> 355
<212> DNA
<213> Homo sapien

<400> 147
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acatttggta tatcttcatt ctttgaaaca caatctatcc ttggcactcc ttcag 355

<210> 148
<211> 369
<212> DNA
<213> Homo sapien

<400> 148
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agggagtgtg ccgagggctt ctgagaaggt ttctctcaca tctagaaaga agcgcttaag 180
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gctgcagcag cctccatcca gcctgaggat gacatcaata cacagaggaa gaagagtcag 300
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acttcttca 369

<210> 149
<211> 620
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(620)
<223> n = A,T,C or G

<400> 149

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gccaatattt ccttatatct atccataaca tttatactac atttgtaana naatatgcac 180
gtgaaactta acactttata aggtaaaaat gaggtttcca anatttaata atctgatcaa 240
gttcttgtta tttccaaata gaatggactt ggtctgttaa gggctaagga gaagaggaag 300
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atgtctctaa gaaagtacta tttcatggtc caaacctggt tgccatantt gggtaaaggc 540
tttcccttaa gtgtgaaant atttaaaatg aaatttttct ctttttaaaa attctttana 600
agggttaagg gtgttgggga 620

<210> 150
<211> 371
<212> DNA
<213> Homo sapien

<400> 150
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ttacttttat a 371

<210> 151
<211> 4655
<212> DNA
<213> Homo sapien

<400> 151
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<210> 152
<211> 586
<212> PRT
<213> Homo sapien

<400> 152

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Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
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Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn
            20                  25                  30
Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
        35                  40                  45
Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
    50                  55                  60
Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
65                  70                  75                  80
His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
                85                  90                  95
Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
            100                 105                 110
Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
        115                 120                 125
Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
    130                 135                 140
Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
145                 150                 155                 160
Glu Gly Gln Ile Ala Pro Ser Ser His Leu Ile Arg Val Glu Gly Asn
                165                 170                 175
Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
            180                 185                 190
Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val
        195                 200                 205
Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg
    210                 215                 220
Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val
225                 230                 235                 240
Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg
                245                 250                 255
Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
            260                 265                 270
Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr
        275                 280                 285
His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp
    290                 295                 300
Glu Leu Val Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu
305                 310                 315                 320
Val Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Leu Gln His
                325                 330                 335
Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu
            340                 345                 350
Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser
        355                 360                 365
Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val
    370                 375                 380
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Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr
385                 390                 395                 400
Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met
                405                 410                 415
Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro
            420                 425                 430
Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro
        435                 440                 445
Tyr Pro Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys
    450                 455                 460
Ser Ser Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr
465                 470                 475                 480
Gln Ile Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro
                485                 490                 495
Glu Gln Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln
            500                 505                 510
Leu His Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser
        515                 520                 525
Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val
    530                 535                 540
Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro
545                 550                 555                 560
Arg Asp Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn
                565                 570                 575
Lys Gln Gln Arg Ile Lys Glu Glu Gly Glu
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<210> 153
<211> 2007
<212> DNA
<213> Homo sapiens

<400> 153

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tggccagggc aattttggag agcaaaaaat ttgcagtgag agcagtgacc agggatgtga    180
cttgaccaaa tgccctggag ctccagcgcc ttggagctga ggtggtcaaa ggtgacctga    240
atgataaagc atcggtggac agtgccttaa aaggtgtcta tggggccttc ttggtgacca    300
actttctggga ccctctcaac caagataagg aagtgtgtcg ggggaagctg gtggcagact   360
ccgccaagca cctgggtctg aagcacgtgg tgtacagcgg cctggagaac gtcaagcgac    420
tgacggatgg caagctggag gtgccgcact ttgacagcaa gggcgaggtg gaggagtact    480
tctggtccat tggcatcccc atgaccagtg tccgcgtggc ggcctacttt gaaaactttc    540
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tgggagatgt accaatggat ggtatctctg ttgctgatat tggagcagcc gtctctagca    660
tttttaattc tccagaggaa tttttaggca aggccgtggg gctcagtgca gaagcactaa    720
caatacagca atatgctgat gttttgtcca aggctttggg gaaagaagtc cgagatgcaa    780
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caccgaagga tttcctgcgg tcgcctcttc agtaggaagc actgcattgg tgataggaca   1140
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agcattggaa atgctaaaat tcagttttgc ctcaagattg gaagtttatt ttctgacttca 1500
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tggcttagca ttttctacat catattgtaa tcgtcttatt tgctagtttt cttccttact 1920
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gttgattgac taaaaaaaaa aaaaaaa 2007

<210> 154
<211> 2148
<212> DNA
<213> Homo sapien

<400> 154
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tggccagggc aattttggag agcaaaaaat ttgcagtgag agcagtgacc agggatgtga 180
cttgaccaaa tgccctggag ctccagcgcc ttggagctga ggtggttaaa ggtgaccttga 240
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cacctgggtc tgaagcacgt ggtgtacagc ggccnggaga acgtcaagcg actgacggat 360
ggcaagctgg aggtgccgca ctttgacagc aagggcgagg tggaggagta cttctggtcc 420
attggcatcc ccatgaccag tgtccgcgtg gcggcctact ttgaaaactt tctcgcggcg 480
tggcggcccg tgaaagcctc tgatggagat tactacacct tggctgtacc gatgggagat 540
gtaccaatgg atggtatctc tgttgctgat attggagcag ccgtctctag cattttaat 600
tctccagagg aatttttagg caaggccgtg gggctcagtg cagaagcact aacaatacag 660
caatatgctg atgttttgtc caaggctttg gggaaagaag tccgagatgc aaagactatc 720
tgtgctatag atgaccagaa aacagtggaa gaaggtttca tggaagacgt gggcttgagt 780
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<210> 155
<211> 153
<212> PRT
<213> Homo sapien

<400> 155
Met Thr Ser Val Arg Val Ala Ala Tyr Phe Glu Asn Phe Leu Ala Ala
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Trp Arg Pro Val Lys Ala Ser Asp Gly Asp Tyr Tyr Thr Leu Ala Val
20 25 30
Pro Met Gly Asp Val Pro Met Asp Gly Ile Ser Val Ala Asp Ile Gly
35 40 45
Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys
50 55 60
Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp
65 70 75 80
Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Ile Thr
85 90 95
Pro Glu Ala Phe Glu Lys Leu Gly Phe Pro Ala Ala Lys Glu Ile Ala
100 105 110
Asn Met Cys Arg Phe Tyr Glu Met Lys Pro Asp Arg Asp Val Asn Leu
115 120 125
Thr His Gln Leu Asn Pro Lys Val Lys Ser Phe Ser Gln Phe Ile Ser
130 135 140
Glu Asn Gln Gly Ala Phe Lys Gly Met
145 150

<210> 156
<211> 128
<212> PRT
<213> Homo sapien

<400> 156
Met Thr Ser Val Arg Val Ala Ala Tyr Phe Glu Asn Phe Leu Ala Ala
1 5 10 15
Trp Arg Pro Val Lys Ala Ser Asp Gly Asp Tyr Tyr Thr Leu Ala Val
20 25 30
Pro Met Gly Asp Val Pro Met Asp Gly Ile Ser Val Ala Asp Ile Gly
35 40 45
Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys
50 55 60
Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp
65 70 75 80
Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Thr Ile
85 90 95
Cys Ala Ile Asp Asp Gln Lys Thr Val Glu Glu Gly Phe Met Glu Asp
100 105 110
Val Gly Leu Ser Trp Ser Leu Arg Glu His Asp His Val Ala Gly Ala
115 120 125

<210> 157
<211> 424
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(424)
<223> n = A,T,C or G

<400> 157
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ggatacatta cagcagacat ggaaatataa ttttaaaaaa tttctctcca acctccttca 120
aattcagtca ccactgttat attaccttct ccaggaaccc tccagtgggg aaggctgcga 180
tattagattt ccttgtatgc aaagtttttg ttgaaagctg tgctcagagg aggtgagagg 240
agaggaagga gaaaactgca tcataacttt acagaattga atctagagtc ttcccccgaaa 300
agcccagaaa cttctctgcn gnatctggct tgtccatctg gtctaaggtg gctgcttctt 360
ccccagccat cgagtcagtt tgtgcccatg aataatacac gacctgctat ttcccatgac 420
tgct 424

<210> 158
<211> 2099
<212> DNA
<213> Homo sapien

<400> 158
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ccgcgcagag cccgcgccag ggcccgccggc cgcagagcag ttaaaacgtg caggcaccag 180
aaggcacttc ctgtcggtga agaagacctg tctccggtgt cacgggcatc ctgtgttttg 240
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tacgcttaag gtggaaagtg ttcattgcac aatatatttt tactgctttc tgaatgtaga 1980

cggaacagtg tggaagcaga aggctttttt aactcatccg tttgccaatc attgcaaaca 2040
actgaaatgt ggatgtgatt gcctcaataa agctcgtccc cattgcttaa aaaaaaaaa 2099

<210> 159
<211> 291
<212> PRT
<213> Homo sapien

<400> 159

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Met Asp Trp Gly Thr Leu His Thr Phe Ile Gly Gly Val Asn Lys His
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            20                  25                  30
Val Met Ile Leu Val Val Ala Ala Gln Glu Val Trp Gly Asp Glu Gln
        35                  40                  45
Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
    50                  55                  60
Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln
65                  70                  75                  80
Leu Ile Phe Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala
                85                  90                  95
Tyr Tyr Arg His Glu Thr Thr Arg Lys Phe Arg Arg Gly Glu Lys Arg
            100                 105                 110
Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys Gln Lys Val Arg Ile
        115                 120                 125
Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Ile
    130                 135                 140
Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Phe Leu Tyr Asn Gly
145                 150                 155                 160
Tyr His Leu Pro Trp Val Leu Lys Cys Gly Ile Asp Pro Cys Pro Asn
                165                 170                 175
Leu Val Asp Cys Phe Ile Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
            180                 185                 190
Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala
        195                 200                 205
Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys Phe Arg Arg Ser Lys Arg
    210                 215                 220
Ala Gln Thr Gln Lys Asn His Pro Asn His Ala Leu Lys Glu Ser Lys
225                 230                 235                 240
Gln Asn Glu Met Asn Glu Leu Ile Ser Asp Ser Gly Gln Asn Ala Ile
                245                 250                 255
Thr Gly Ser Gln Ala Lys His Phe Lys Val Lys Cys Ser Cys Val Ile
            260                 265                 270
Arg Arg Leu Leu Ser Ser Pro Glu Gly Asn Thr Asn Leu Lys Val Pro
        275                 280                 285
Ser Val Ala
    290
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<210> 160
<211> 3951
<212> DNA
<213> Homo sapien

<400> 160
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tgtgactctc ctggttgcct taagttcaga actcccattc ctgggagctg gagtacagct     180
tcaagacaat gggtataatg gattgctcat tgcaattaat cctcaggtac ctgagaatca     240
gaacctcatc tcaaacatta aggaaatgat aactgaagct tcattttacc tatttaatgc     300
taccaagaga agagtatttt tcagaaatat aaagatttta atacctgcca catggaaagc     360
taataataac agcaaaataa aacaagaatc atatgaaaag gcaaatgtca tagtgactga     420
ctggtatggg gcacatggag atgatccata cacactacaa tacagagggt gtggaaaaga     480
gggaaaatac attcatttca cacctaattt cctactgaat gataacttaa cagctggcta     540
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atgggatgta atcacagact ctgctgactt tcaccacagc tttcccatga acgggactga     960
gctttccacct cctcccacat tctcgcttgt agaggctggt gacaaagtgg tctgtttagt    1020
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agaattttat ttgatgcaga ttgttgaaat tcataccttc gtgggcattg ccagtttcga    1140
cagcaaagga gagatcagag cccagctaca ccaaattaac agcaatgatg atcgaaagtt    1200
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tcgcgcctcc aactcagctg tgccccagc cactgtggaa gcctttgtgg aaagagacag    1920
cctccatttt cctcatcctg tgatgattta tgccaatgtg aaacagggat tttatcccat    1980
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cagcataagc accccagccc actctattcc agggagtcat gctatgtatg taccaggtta    2220
cacagcaaac ggtaatattc agatgaatgc tccaaggaaa tcagtaggca gaaatgagga    2280
ggagcgaaag tggggcttta gccgagtcag ctcaggaggc tccttttcag tgctgggagt    2340
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ccaggctaca agctatgaaa taagaatgag taaaagtcta cagaatatcc aagatgactt    2520
taacaatgct attttagtaa atacatcaaa gcgaaatcct cagcaagctg gcatcaggga    2580
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gtctgctgta tctaacattg cccaggcgcc tctgtttatt ccccccaatt ctgatcctgt    2760
acctgccaga gattatctta tattgaaagg agttttaaca gcaatgggtt tgataggaat    2820
catttgcctt attatagttg tgacacatca tactttaagc aggaaaaaga gagcagacaa    2880
gaaagagaat ggaacaaaat tattataaat aaatatccaa agtgtcttcc ttcttagata    2940
taagacccat ggccttcgac tacaaaaaca tactaacaaa gtcaaattaa catcaaaact    3000
gtattaaaat gcattgagtt tttgtacaat acagataaga tttttacatg gtagatcaac    3060
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aattatttct taaagtaatg tctttaaagg caaagggaag ggtaaagtcg gaccagtgtc    3180
aaggaaagtt tgttttattg aggtggaaaa atagccccaa gcagagaaaa ggagggtagg    3240
tctgcattat aactgtctgt gtgaagcaat catttagtta ctttgattaa ttttttcttt    3300
ctcctttatct gtgcagaaca ggttgctttgt ttacaactga agatcatgct atatttcata    3360
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tatgaagccc ctaatgcaaa gctctttacc tcttgctatt ttgttatata tattacagat 3420
gaaatctcac tgctaatgct cagagatctt ttttcactgt aagaggtaac ctttaacaat 3480
atgggtatta ccttttgtctc ttcataccgg ttttatgaca aaggtctatt gaatttattt 3540
gtttgtaagt ttctactccc atcaaagcag ctttttaagt tattgccttg gttattatgg 3600
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<210> 161
<211> 943
<212> PRT
<213> Homo sapien

<400> 161

Met Thr Gln Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val
1 5 10 15
Thr Leu Leu Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly
20 25 30
Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
35 40 45
Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
50 55 60
Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
65 70 75 80
Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
85 90 95
Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
100 105 110
Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
115 120 125
Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
130 135 140
Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
145 150 155 160
Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
165 170 175
Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
180 185 190
Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
195 200 205
Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
210 215 220
Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
225 230 235 240
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
245 250 255
Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
260 265 270
Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser
275 280 285
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu
290 295 300

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Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser
305                 310                 315                 320
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu
                325                 330                 335
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala
            340                 345                 350
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn
        355                 360                 365
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val
    370                 375                 380
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe
385                 390                 395                 400
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile
                405                 410                 415
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr
            420                 425                 430
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser
        435                 440                 445
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys
    450                 455                 460
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe
465                 470                 475                 480
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
                485                 490                 495
Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
            500                 505                 510
Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
        515                 520                 525
Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
    530                 535                 540
Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
545                 550                 555                 560
Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
                565                 570                 575
Tyr Thr Leu Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr
            580                 585                 590
Val Thr Ser Arg Ala Ser Asn Ser Ala Val Pro Pro Ala Thr Val Glu
        595                 600                 605
Ala Phe Val Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile
    610                 615                 620
Tyr Ala Asn Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val
625                 630                 635                 640
Thr Ala Thr Val Glu Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu
                645                 650                 655
Leu Asp Asp Gly Ala Gly Ala Asp Val Ile Lys Asn Asp Gly Ile Tyr
            660                 665                 670
Ser Arg Tyr Phe Phe Ser Phe Ala Ala Asn Gly Arg Tyr Ser Leu Lys
        675                 680                 685
Val His Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile
    690                 695                 700
Pro Gly Ser His Ala Met Tyr Val Pro Gly Tyr Thr Ala Asn Gly Asn
705                 710                 715                 720
Ile Gln Met Asn Ala Pro Arg Lys Ser Val Gly Arg Asn Glu Glu Glu
                725                 730                 735
Arg Lys Trp Gly Phe Ser Arg Val Ser Ser Gly Gly Ser Phe Ser Val
```

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            740                 745                 750
Leu Gly Val Pro Ala Gly Pro His Pro Asp Val Phe Pro Pro Cys Lys
        755                 760                 765
Ile Ile Asp Leu Glu Ala Val Lys Val Glu Glu Leu Thr Leu Ser
    770                 775                 780
Trp Thr Ala Pro Gly Glu Asp Phe Asp Gln Gly Gln Ala Thr Ser Tyr
785                 790                 795                 800
Glu Ile Arg Met Ser Lys Ser Leu Gln Asn Ile Gln Asp Asp Phe Asn
                805                 810                 815
Asn Ala Ile Leu Val Asn Thr Ser Lys Arg Asn Pro Gln Gln Ala Gly
            820                 825                 830
Ile Arg Glu Ile Phe Thr Phe Ser Pro Gln Ile Ser Thr Asn Gly Pro
        835                 840                 845
Glu His Gln Pro Asn Gly Glu Thr His Glu Ser His Arg Ile Tyr Val
    850                 855                 860
Ala Ile Arg Ala Met Asp Arg Asn Ser Leu Gln Ser Ala Val Ser Asn
865                 870                 875                 880
Ile Ala Gln Ala Pro Leu Phe Ile Pro Pro Asn Ser Asp Pro Val Pro
                885                 890                 895
Ala Arg Asp Tyr Leu Ile Leu Lys Gly Val Leu Thr Ala Met Gly Leu
            900                 905                 910
Ile Gly Ile Ile Cys Leu Ile Ile Val Val Thr His His Thr Leu Ser
        915                 920                 925
Arg Lys Lys Arg Ala Asp Lys Lys Glu Asn Gly Thr Lys Leu Leu
    930                 935                 940
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<210> 162
<211> 498
<212> DNA
<213> Homo sapien

<400> 162

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accggcagat gggcaagggt ggcaagcatc accttggcct ggaggagccc aagaagctgc     180
gaccaccccc tgccaggact ccctgccaac aggaactgga ccaggtcctg gagcggatct     240
ccaccatgcg ccttccggat gagcggggcc ctctggagca cctctactcc ctgcacatcc     300
ccaactgtga caagcatggc ctgtacaacc tcaaacagtg gcaagatgtc tctgaacggg     360
cagcgtgggg agtgctggtg tgtgaacccc aacaccggga agctgatcca gggagccccc     420
accatccggg gggaccccga gtgtcatctc ttctacaatg agcagcagga ggctcgcggg     480
gtgcacaccc cagcggat                                                   498
```

<210> 163
<211> 1128
<212> DNA
<213> Homo sapien

<400> 163

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aatcaacttt ccggaagcaa ccagcccacc agaggaggtc ccgagcgcga gcggagacga     120
tgcagcggag actggttcag cagtggagcg tcgcggtgtt cctgctgagc tacgcggtgc     180
cctcctgcgg gcgctcggtg gagggtctca gccgccgcct caaaagagct gtgtctgaac     240
atcagctcct ccatgacaag gggaagtcca tccaagattt acggcgacga ttcttccttc     300
accatctgat cgcagaaatc cacacagctg aaatcagagc tacctcggag gtgtcccctg     360
actccaagcc ctctcccaac acaaagaacc accccgtccg atttgggtct gatgatgagg     420
```

gcagatacct aactcaggaa actaacaagg tggagacgta caaagagcag ccgctcaaga 480
cacctgggaa gaaaaagaaa ggcaagcccg ggaaacgcaa ggagcaggaa aagaaaaaac 540
ggcgaactcg ctctgcctgg ttagactctg gagtgactgg gagtgggcta gaaggggacc 600
acctgtctga cacctccaca acgtcgctgg agctcgattc acggaggcat tgaaattttc 660
agcagagacc ttccaaggac atattgcagg attctgtaat agtgaacata tggaaagtat 720
tagaaatatt tattgtctgt aaatactgta aatgcattgg aataaaactg tctccccccat 780
tgctctatga aactgcacat tggtcattgt gaatattttt ttttttgcca aggctaatcc 840
aattattatt atcacattta ccataattta ttttgtccat tgatgtattt attttgtaaa 900
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tatcaagtat gttgataaat gacacaatga agtgtctcta ttttgtggtt gattttaatg 1020
aatgcctaaa tataattatc caaattgatt ttcctttgtg catgtaaaaa taacagtatt 1080
ttaaatttgt aaagaatgtc taataaaata taatctaatt acatcatg 1128

<210> 164
<211> 1310
<212> DNA
<213> Homo sapien

<400> 164
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gagacgtgta aacacactac ttatcattga tgcatatata aaaccatttt attttcgcta 180
ttatttcaga ggaagcgcct ctgatttgtt tctttttttcc cttttgctc tttctggctg 240
tgtggtttgg agaaagcaca gttggagtag ccggttgcta aataagtccc gagcgcgagc 300
ggagacgatg cagcggagac tggttcagca gtggagcgtc gcggtgttcc tgctgagcta 360
cgcggtgccc tcctgcgggc gctcggtgga gggtctcagc cgccgcctca aaagagctgt 420
gtctgaacat cagctcctcc atgacaaggg gaagtccatc caagatttac ggcgacgatt 480
cttccttcac catctgatcg cagaaatcca tacagctgaa atcagagcta cctcggaggt 540
gtcccctaac tccaagcccc ctcccaacac aaagaaccac cccgtccgat ttgggtctga 600
tgatgagggc agatacctaa ctcaggaaac taacaaggtg gagacgtaca aagagcagcc 660
gctcaagaca cctgggaaga aaaagaaagg caagcccggg aaacgcaagg agcaggaaaa 720
gaaaaaacgg cgaactcgct ctgcctggtt agactctgga gtgactggga gtgggctaga 780
aggggaccac ctgtctgaca cctccacaac gtcgctggag ctcgattcac ggaggcattg 840
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ttttaatgaa tgcctaaata taattatcca aattgatttt cctttgtgcc cgtaaaaata 1260
acagtatttt aaatttgtaa agaatgtcta ataaaatata atctaattac 1310

<210> 165
<211> 177
<212> PRT
<213> Homo sapien

<400> 165
Met Gln Arg Arg Leu Val Gln Gln Trp Ser Val Ala Val Phe Leu Leu
1 5 10 15
Ser Tyr Ala Val Pro Ser Cys Gly Arg Ser Val Glu Gly Leu Ser Arg
20 25 30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
35 40 45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile

```
    50                  55                  60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65                  70                  75                  80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
                85                  90                  95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
            100                 105                 110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Lys Gly
        115                 120                 125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
    130                 135                 140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145                 150                 155                 160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg Arg
                165                 170                 175
His
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<210> 166
<211> 177
<212> PRT
<213> Homo sapien

<400> 166

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Met Gln Arg Arg Leu Val Gln Gln Trp Ser Val Ala Val Phe Leu Leu
 1               5                  10                  15
Ser Tyr Ala Val Pro Ser Cys Gly Arg Ser Val Glu Gly Leu Ser Arg
            20                  25                  30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
        35                  40                  45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
    50                  55                  60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65                  70                  75                  80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
                85                  90                  95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
            100                 105                 110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Lys Gly
        115                 120                 125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
    130                 135                 140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145                 150                 155                 160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg Arg
                165                 170                 175
His
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<210> 167
<211> 3362
<212> DNA
<213> Homo sapien

<400> 167

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ttcagaactc ccattcctgg gagctggagt acagcttcaa gacaatgggt ataatggatt 180
gctcattgca attaatcctc aggtacctga gaatcagaac ctcatctcaa acattaagga 240
aatgataact gaagcttcat tttacctatt taatgctacc aagagaagag tatttttcag 300
aaatataaag attttaatac ctgccacatg gaaagctaat aataacagca aaataaaaca 360
agaatcatat gaaaaggcaa atgtcatagt gactgactgg tatggggcac atggagatga 420
tccatacacc ctacaataca gagggtgtgg aaaagaggga aaatacattc atttcacacc 480
taatttccta ctgaatgata acttaacagc tggctacgga tcacgaggcc gagtgtttgt 540
ccatgaatgg gcccacctcc gttggggtgt gttcgatgag tataacaatg acaaaccttt 600
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gctctgtttt ttggttaaat aagagtcttt aatccttttt ccatcaagag ttacttacca 3240
agggcagggg aaggggata tagaggtcac aaggaaataa aaatcatctt tcatctttaa 3300

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tt 3362

<210> 168
<211> 2784
<212> DNA
<213> Homo sapien

<400> 168
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tgtgactctc ctggttgcct taagttcaga actcccattc ctgggagctg gagtacagct 180
tcaagacaat gggtataatg gattgctcat tgcaattaat cctcaggtac ctgagaatca 240
gaacctcatc tcaaacatta aggaaatgat aactgaagct tcattttacc tatttaatgc 300
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taataataac agcaaaataa aacaagaatc atatgaaaag gcaaatgtca tagtgactga 420
ctggtatggg gcacatggag atgatccata caccctacaa tacagagggt gtggaaaaga 480
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ctgtattatt agtaagcttt ttaaagaagg atgcaccttt atctacaata gcacccaaaa 780
tgcaactgca tcaataatgt tcatgcaaag tttatcttct gtggttgaat tttgtaatgc 840
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agaattttat ttgatgcaga ttgttgaaat tcataccttc gtgggcattg ccagtttcga 1140
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, A61K 38/17, C07K 14/47, 16/18, A61K 35/14

A3

(11) International Publication Number: WO 99/47674

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09/123,933	27 July 1998 (27.07.98)	US

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(74) Agents: MAKI, David, J. et al.; Seed and Berry LLP, 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
20 January 2000 (20.01.00)

(54) Title: COMPOUNDS AND METHODS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER

(57) Abstract

Compounds and methods for the treatment and diagnosis of lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or DNA molecules encoding such polypeptides, are also provided, together with DNA molecules for preparing the inventive polypeptides.

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INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 99/05798

A. CLASSIFICATI N OF SUBJECT MATTER
IPC 6 C12N15/12 A61K38/17 C07K14/47 C07K16/18 A61K35/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRASS N ET AL: "Translation initiation factor eIF-4gamma is encoded by an amplified gene and induces animmune response in squamous cell lung carcinoma" HUMAN MOLECULAR GENETICS., vol. 6, no. 1, January 1997 (1997-01), pages 33-39, XP002112603 OXFORD UNIVERSITY PRESS, SURREY., GB ISSN: 0964-6906 page 34, left-hand column, paragraph 2 -right-hand column --- -/--	1-7,15, 24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1999	06.12.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	CUPIDO, M

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INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 99/05798

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FINCH J ET AL.: "Identification of a cloned sequence activated during multi-stage carcinogenesis in mouse skin" CARCINOGENESIS, vol. 12, no. 8, August 1991 (1991-08), pages 1519-1522, XP002112604 the whole document	1-7,15, 24
X	Database EMBLest17 Sequence HSW22264:human retina cDNA Tsp509I. 9 May 1996 compare nucleotides 242-1 with the complement of nucleotides 1-232 in SEQ ID NO:1 XP002112605 nucleotides 1-242	1
X	Database EMBLest17 Sequence AA340797: EST46165 fetal kidney homo sapiens cDNA 3' end: 18 April 1997 compare nucleotides 111-305 with the inverse complement of nucleotides 107-299 in SEQ ID NO:1 XP002112606 nucleotides 111-305	1
A	WO 96 30389 A (MILLENIUM PHARMACEUTICALS INC) 3 October 1996 (1996-10-03) page 112 -page 127	1-11, 15-58
A	WO 96 02552 A (BOLLON ARTHUR P ;CYTOCLONAL PHARMACEUTICS INC (US); TORCZYNSKI RIC) 1 February 1996 (1996-02-01) the whole document	1-11, 15-58

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INTERNATIONAL SEARCH REPORT

I. .national application No.

PCT/US 99/05798

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 15, 16, 22, 23, 29, 30, 46-51 and 54-56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11, 15-58 (all partly and as far as applicable)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-11, 15-58 (all partly and as far as applicable)

Polynucleotides comprising the sequence provided in SEQ ID NO:1, their complement sequences, variants thereof, corresponding polypeptides, vectors, pharmaceutical compositions, vaccines, their applications, fusion proteins, diagnostics, antibodies, diagnostic kits and their use in diagnosis and treatment of lung cancer.

2-160. Claims: 1-58 (all partly and as far as applicable)

Idem as invention 1 but limited to each of the DNA sequences provided in SEQ ID NO: 2-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168 and 171.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Inter nal Application No
PCT/US 99/05798

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